NHS National Services Scotland

Transmission Based Precautions (TBPs) Definitions Literature Review

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ARHAI Scotland
Antimicrobial Resistance and Healthcare Associated Infection

Key Information

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Document information	Description
Description:	This literature review examines the available professional literature on transmission-based precaution definitions in the healthcare setting.
Purpose:	To inform the National Infection Prevention and Control Manual in order to facilitate the prevention and control of healthcare associated infections in NHSScotland health and care settings.
Target Audience:	All staff involved in the prevention and control of infection in NHSScotland.
Update/review schedule	Monthly review of published literature via autoalert searches of Medline and Embase databases. Updated as new evidence emerges with changes made to recommendations as required. Review will be formally updated every 3 years with next review in 2026.
Cross reference:	National Infection Prevention and Control Manual

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Version history

This literature review will be updated in real time if any significant changes are found in the professional literature or from national guidance/policy.

Version	Date	Summary of changes
1.0	19 August 2024	New literature review with revised research questions and search strategy. Assessment of evidence from January 2000 to April 2022. Previous literature review (titled 'Transmission Based Precautions Literature Review: Definitions of Transmission Based Precautions' version 3.0 published October 2020) will be archived once recommendations from this literature review have been finalised.

Approvals

Version	Date Approved	Name
1.0	27 April 2023	National Policies Guidance and Evidence Working Group
1.0	27 April 2023	Community Infection Prevention and Control Working Group

Contents

1. Research Questions

The aim is to review the extant scientific literature regarding transmission-based precautions (TBPs) definitions in health and care settings to inform evidence-based recommendations for practice. The specific research questions of the review are:

1. What is the current definition of contact transmission?
2. What is the current definition of droplet transmission?
3. What is the current definition of airborne transmission?
4. How are infectious agents released into the air of the health and care environment from the respiratory tract with consideration of particle size, distance and clearance/fallout time?
5. Can person-to-person transmission of infection be described/defined beyond the current categories of contact/droplet and/or airborne?
6. What are transmission-based precautions (TBPs)?
7. When should TBPs be applied?
8. Are there reported occurrences of person-to-person pathogen transmission which do not align with their currently assigned transmission mode(s)?
9. What factors should be considered when determining whether to discontinue TBPs?

2. Methodology

This targeted literature review was produced using a defined systematic methodology as described in the **National Infection Prevention and Control Manual (NICPM): Development Process**. Three academic databases were searched on 9 May 2022 for relevant studies: Medline, Embase and CINAHL (Cumulative Index to Nursing and Allied Health Literature). Grey literature searching was conducted using a number of relevant online sites which are detailed in the **NIPCM development process**. Reference lists of included articles were also screened.

2.1 Search Strategy

1. "transmission based precaution*".mp.
2. "additional infection control*".mp.
3. "airborne transmission*".mp.
4. "droplet transmission*".mp
5. "contact transmission*".mp.
6. airborne.mp.
7. droplet*.mp.
8. "contact precaution*".mp.
9. exp Aerosols/
10. aerosol*.mp.
11. "fomite transmission*".mp.
12. Fomites/
13. fomite*.mp.
14. “additional precaution*”.mp
15. “special precaution*”.mp
16. “enhanced control measure*”.mp
17. bioaerosol*.mp
18. exp Infection Control/
19. exp Disease Transmission, Infectious/
20. exp infections/ or exp cross infection/ or exp opportunistic infections/
21. 18 or 19 or 20
22. ((termin* or end* or cease* or ceasing or stop* or discontinu* or finish*) adj3 ("transmission based precaution*" or "additional infection control*" or "airborne precaution*" or "droplet precaution*" or "contact precaution*" or “additional precaution*” or “special precaution*” or “enhanced control measure*”)).mp.
23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
24. "environmental contaminat*".mp.

25. "environmental sampl*".mp. or Environmental Monitoring/
26. ("health care setting*" or "healthcare setting*" or hospital* or "care home*").mp.
27. exp Health Facilities/
28. 24 or 25
29. 26 or 27
30. 21 and 28 and 29
31. 21 and 23
32. 22 or 30 or 31
33. limit 32 to (english language, human studies and yr="2000 - 2023")
34. Aerosols/
35. "Respiratory Aerosols and Droplets"/
36. (aerosol* or bioaerosol* or particle*).mp
37. 34 or 35 or 36
38. ("respiratory tract*" or breath* or speaking or speech or talk* or sneez* or cough* or sing* or spit* or shout* or AGP or "aerosol generating procedure*" or "medical procedure*" or "dental procedure*" or “surgical procedure*” or surgery or surgeries or dentistry).mp
39. exp Pharmaceutical Preparations/
40. exp "Nebulizers and Vaporizers"/
41. (drug* or medicine* or medicinal* or inhaler*).mp
42. 37 and 38
43. 42 not (39 or 40 or 41)
44. 33 or 43
45. limit 44 to (english language, human studies and yr="2000 - 2023")

2.2 Exclusion criteria

In addition to the exclusion criteria outlined in the **NIPCM: Development Process** the following study types were excluded for this review:

- Air sampling studies which only detected the presence of bacterial or viral RNA/DNA in the air without inclusion of secondary data such as distance of detection, particle sizes or exploration of correlations.
- Air sampling studies in which the source of airborne pathogens and/or particles was unclear, for example, results from sampling in the centre of a general ward with unknown numbers of patients, staff and visitors contributing to samples.
- Outbreak reports where unconventional modes of transmission were reported if associated with a non-healthcare setting (research question 8).
- In relation to guidance or expert opinion, pathogen specific guidance was excluded. General IPC guidance and guidance on groups of pathogens/infections, such as multi-drug resistant organisms (MDRO) or acute respiratory infection (ARI) guidance, was included.
- Air sampling studies which assessed particle production during medical or care procedures were excluded if they did not involve the respiratory tract.
- Systematic reviews without meta-analyses.
- Mask sampling studies where the fabric or surface of a surgical mask or respirator was analysed for presence of pathogens.
- Studies that used visual assessment of particle production/aerosol spread for example using smoke or fluorescent stained droplets.
- Studies which assessed particle production/spread from non-respiratory tract sources for example those produced during vomiting or diarrhoeal episodes.
- Studies involving mathematical modelling or computational fluid dynamics.

A PRISMA flowchart is presented in **Appendix 2**. Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

2.3 Critical appraisal

Identified studies and guideline documents were critically appraised and graded using the SIGN 50 methodology and AGREE tool as per the **NIPCM: Development Process.** **Appendix 1** outlines the SIGN 50 grading system for evidence appraisal.

Evidence tables were compiled summarising each item of evidence and its impact on, or contribution to, the specified research question. Evidence tables are used in conjunction with the **considered judgement form** to provide a narrative summary of the evidence. At this stage in the process, only Part A of the considered judgement form has been completed which summarises the volume, consistency, applicability, and generalisability of the available evidence. Part B of the considered judgement form will be completed with the NPGE Working Group during development of recommendations.

2.4 Consultation

This literature review was sent to the following individuals and groups for comment as part of the consultation process:

- ARHAI Scotland National Policies Guidance and Evidence Working Group (networks and organisations represented in this working group are detailed within the **NIPCM: development process**)
- ARHAI Scotland Community Infection Prevention and Control Working Group (networks and organisations represented in this group are detailed within the **NIPCM: development process**)
- Public Health Scotland (PHS) Scottish Health Protection Network (SHPN) TB Network

Four external subject matter experts engaged with the consultation process and provided comment on this literature review. ARHAI Scotland would like to thank Professor Lidia Morawska, Professor Hilary Humphreys, Professor Yuguo Li and Professor Ben Cowling.

The following individuals and groups were sighted on this literature review during the consultation phase:

- Scottish Chief Dental Officer
- Scottish Chief Medical Officer
- Scottish Chief Nursing Officer
- Scottish Deputy Chief Nursing Officer
- NHS England
- NHS Wales
- Health and Social Care Northern Ireland
- Scottish Healthcare Associated Infection (HAI) executive leads
- Scottish NHS board directors
- Public Health Scotland (PHS) (including PHS Public Health Microbiology, PHS Dental and PHS Respiratory)
- Scottish Perinatal network
- Scottish Intensive Care Society Audit Group (SICSAG)
- Scottish Dental Clinical Effectiveness Programme (SDCEP)

3. Discussion

3.1 Introduction

For decades the description of how infectious agents are spread from person-to-person has been based on three transmission terms: contact, droplet and airborne. The perceived predominant transmission mode of an infectious agent (contact, droplet or airborne) currently indicates the group of specific measures that are designed to prevent and control the spread of its associated infection. Over time, acknowledgement of the multiple factors which influence transmission mode, alongside clear inadequacy of the droplet/airborne dichotomy, have indicated a requirement for reassessment of this framework.

3.2 What is the current definition of contact transmission?

Thirteen pieces of organisational expert opinion were included for this research question. Alongside two World Health Organization guidance documents[1, 2] other SIGN50 level 4 guidance was considered from six countries: the U.S.A,[3-5] Australia,[6, 7] New Zealand,[8] England,[9, 10] Hong Kong,[11] Canada[12] and Northern Ireland.[13]

Most sources outlined that contact transmission can be considered as either direct or indirect.[1-3, 6-13]

Direct contact transmission is defined as the physical transfer of infectious agents from an infected or colonised person to another susceptible individual, via touch[1, 2, 11, 12] or contact with blood or bodily substances[7, 13] without a contaminated intermediate object or person.[3, 6, 7]

Examples of opportunities for transmission via direct contact are provided by some sources, these include; mucous membranes or broken skin coming into contact with blood-containing body fluids,[3, 7] the transfer of herpes simplex virus via herpetic whitlow lesion contact,[3] contact with the hands of a person who has coughed into them followed by inadequate hand hygiene and transfer to mucous membranes (mouth, nose, eyes),[9] shaking hands[12] and patient-care activities that require touching the patient's skin, secretions or body fluids.[13]

Indirect contact transmission is defined as the transfer of an infectious agent to a susceptible host via a contaminated intermediate object.[1-3, 6, 7, 12]

Examples of vectors for indirect contact transmission are provided by some sources and include healthcare worker hands,[3, 9, 12] patient care equipment,[3, 9, 12, 13] shared toys,[3, 12] computers,[12] inadequately cleaned and/or sterilised medical instruments[3] and environmental surfaces for example furniture, bedrails.[8, 9, 12] Specific examples for indirect contact transmission opportunities include; contact with surfaces that infected persons have coughed or sneezed on followed by inadequate hand hygiene and subsequent mucous membrane contact,[9] inadequate hand hygiene by healthcare workers who have touched a patient's infected body site, faeces and/or contaminated bedding then provided care for a susceptible patient[7] and contact with

surfaces that are not appropriately cleaned or have defects that prevent adequate cleaning followed by inadequate hand hygiene and care of a susceptible patient.[12]

New Zealand guidance does not specifically use the terms direct or indirect contact transmission but states that infectious agents can be spread from person to person "directly through close contact" or "indirectly from an infected person to an object […] and then to another person who comes into contact with the contaminated item".[8]

Examples of pathogens spread by contact transmission are presented in most sources. They include *Clostridioides difficile (C.difficile),*[3-5, 7, 11-13] multi-drug resistant organisms such as Methicillin resistant *Staphylococcus aureus* (MRSA), Carbapenemase producing organisms (CPOs), extended-spectrum beta-lactamases (ESBLs) and Vancomycin resistant enterococci (VRE),[3-5, 7, 8, 12, 13] Norovirus,[3, 4, 7, 11, 13] herpes simplex virus,[3] *Staphylococcus aureus,*[1, 3, 13] *Escherichia coli,*[1] Salmonella,[13] respiratory syncytial virus (RSV),[3, 7] *Klebsiella pneumoniae*[1] and Ebola virus.[1] Some sources provided a more general description of the types of pathogens transmitted via contact. These general descriptions included; "pathogens which cause highly contagious skin infections or infestations"[7] and "intestinal tract pathogens",[3, 7] food poisoning organisms,[13] or similarly, gastrointestinal pathogens that cause diarrhoea and/or gastroenteritis.[1, 12]

Three sources provided citations to support their definitions and examples of contact transmission. The CDC,[3] Australian National Health and Medical Research Council (NHMRC)[7] and Canadian Public Health Agency (PHA)[12] cited environmental sampling studies which demonstrated the transfer of infectious agents from surfaces to healthcare worker hands and from their hands onto surfaces.[14-16] CDC[3] and Australian guidance[7] both cited outbreak reports; one which suggested spread of infection via contaminated surfaces in an inadequately cleaned theatre space following a Norwalk-like virus related vomiting episode[17] and two outbreak investigations where matching environmental and clinical isolates were identified, with one presenting results of a risk factor analysis to support their environmental source hypothesis.[18, 19] To support descriptions of both indirect and direct contact transmission, the CDC[3], Australian NHMRC[7] and Canadian Public Health Agency[12] all cited an experimental 1981 infection study where RSV was transmitted from hospitalised infants to volunteers who touched the infants' surroundings, followed by

their own mucous membranes (n=4/10), but those who sat >6ft (>approx. 2m) from the infants (n=14) (and did not touch the infants or their surroundings) did not become infected.[20] The CDC[3] cited blood borne virus, *Mycobacterium tuberculosis* and *Pseudomonas aeruginosa* transmission reports, for which genetic sequencing and/or epidemiological evidence supported indirect transmission via patient care devices.[21-27] To further support the concept of indirect transmission, Canadian[12] and CDC[3] guidance cited before-after studies where changes to equipment types (for example a switch to disposable patient care equipment)[28] or implementation of specific equipment cleaning protocols[29] resulted in reduced nosocomial infection rates, however, for all these studies there is a significant risk that the observed effects were not related specifically to the implementations alone. To support the concept of contact transmission, Canadian guidance[12] cited two experimental studies where infection occurred in volunteers via mucosal exposure only, although both sources of contamination were artificial in nature (inoculation/seeding of surfaces).[30, 31] Canadian guidance[12] cited three small environmental sampling studies where authors had identified contamination of healthcare setting computer equipment with varied pathogens.[32-34] In one of these studies, clinical patient MRSA isolates were matched with environmental samples from both within and out with the patient room,[34] however, these studies do not definitively confirm indirect transmission.

3.3 What is the current definition of droplet transmission?

Fourteen pieces of organisational expert opinion were included for this research question. Alongside two World Health Organization guidance documents[1, 2] other SIGN50 level 4 guidance was considered from eight countries; Canada,[12] Australia,[6, 7] New Zealand,[8] Ireland,[35] England,[9, 10] Hong Kong,[11] Northern Ireland,[13] and the U.S.A.[3, 5, 36]

In the literature, droplet transmission is defined as the process of infectious respiratory droplets travelling over 'short' distances, from the respiratory tract of an infectious individual directly through the air, to the susceptible mucosal surfaces (eyes, mouth and/or nose) of the recipient.[1-3, 6, 7, 9, 10, 12]

The definition of droplet transmission is not always limited to the air-mediated projection of particles described above. Throughout the literature, there is an unclear delineation between contact and droplet transmission definitions. Canadian, New Zealand and Australian guidance reflect the concept of an expanded droplet transmission definition by stating that droplet transmission can indeed occur through expulsion of droplets directly onto a susceptible person's mucosa, but that it can also be defined by transfer of infectious agents to mucosal surfaces, via respiratory droplet contaminated surfaces and hands.[7, 8, 12] The CDC state that droplet transmission can be considered a form of contact transmission[3] with an Australian droplet precautions poster highlighting that "droplets can contaminate horizontal surfaces close to the source patient, and the hands of healthcare workers can become contaminated through direct contact with those surfaces".[6] The WHO, however, maintain the delineation between the two transmission modes of contact and droplet, stating that for some pathogens both routes are possible; "In addition to transmission by large droplets, some common respiratory pathogens […] can be transmitted through contact – particularly by hand contamination and self-inoculation into conjunctival or nasal mucosa".[2]

Canadian guidance[12] describes droplets as "solid or liquid particles suspended in the air". Current guidance commonly describes the respiratory particles involved in droplet transmission, as being equal to or greater than 5μm in size, with almost all lacking supportive citations.[3, 5-7, 11] The CDC[3] cite a 1946 paper by Duguid et al. which does not specifically identify particles of >5μm as being associated with droplet transmission but rather cites another paper which postulated that "most particles larger than 5μm in diameter are deposited by centrifugal force in the upper respiratory tract (nasal cavity), while many particles smaller than 5μm are deposited by settlement in the alveoli of the lungs".[37] Duguid et al cites Wells (1934)[38] who provided estimations for 2 metre particle drop times in saturated air for example 10 minutes for 10μm particles.[37] In contrast to most guidance, Canadian guidance authors outline droplets as being greater than 10μm.[12] English social care guidance simply uses the term 'larger droplets'[10] and Australian guidance describes droplet transmission particles as "intermediate in size between drops and droplet nuclei".[7]

English guidance specifies that droplets enter the upper respiratory tract[10] whilst New Zealand guidance was the only source to describe inhalation of droplets stating that they "may be breathed in by people who are near".[8]

Many guidance documents state that droplets are generated when an infected person coughs, sneezes, or talks.[1-3, 5-9, 11-13, 35] Whilst Irish, American, Northern Irish and Australian guidance also includes descriptions of droplet production during certain medical procedures[7] such as suctioning,[3, 35] endotracheal intubation, cough induction by chest physiotherapy, cardiopulmonary resuscitation,[3] sputum induction, "treatment of lesions/abscesses when aerosolisation of drainage fluid is anticipated"[35] and nebulisation.[13, 35] Australian guidance also describes shower related droplet production; "when water is converted to a fine mist by an aerator or shower head".[7]

Authors suggest that when considering a specific pathogen, one way in which droplet transmission can be distinguished from airborne transmission is through assessment of evidence for transmission over certain distances.[3] The CDC state that organisms transmitted by the droplet route do not remain infective over long distances[3] whilst Australian, English, Hong Kong, Canadian and WHO guidance specifies that, due to gravitational forces, droplets do not remain suspended in the air for long, and therefore cannot traverse large distances.[1, 2, 6-9, 11, 12] Most sources do not provide citations to support these concepts, however Canadian guidance[12] does cite a 2007 modelling study where the historical Wells evaporation–falling curve is reconsidered factoring in the effects of humidity, air speed, and respiratory jets.[39] Based on calculations, authors estimated that 'large droplets' (approximately 60-125µm in size) could be carried >6m away by sneezing, >2m away by coughing and <1m by breathing;[39] this somewhat contradicts the guidance statement it is cited to support, where droplet transmission is associated with 'short' distances.[12]

The CDC state that, based on epidemiologic and simulated studies, the area of risk for droplet transmission has been reported as up to 3ft (0.91m) around the infected individual.[3] They cite a 1981 school classroom-based *Neisseria meningitidis* outbreak investigation with significant limitations[40] and an experimental infection study where rhinovirus infected individuals played poker with susceptible persons.[41] The outbreak investigation cannot support the notion of predominant or sole spread

of *N. meningitidis* via close proximity/contact[40] and the experimental study can only provide evidence for short range air-mediated transmission, it does not rule out long range transmission or highlight a specific 'at-risk' area.[41] Similar to the CDC, WHO guidance outlines that droplets are usually propelled <1m.[2] English, Australian and Canadian guidance report a greater, but not dissimilar, at-risk distance of <1-2m.[7, 9, 12] The CDC report that donning masks, using a 3ft (0.91m) distance trigger, has prevented transmission, however, no citations are provided.[3] The CDC outline that "the maximum distance for droplet transmission is currently unresolved" but that "pathogens transmitted by the droplet route have not been transmitted through the air over long distances, in contrast to […] airborne pathogens".[3] In summation, English and Australian guidance[6, 7, 9] outlines that physical closeness is required for droplet transmission, however, this would not align with a droplet transmission definition which also incorporated touching of environmental surfaces as described in Canadian, Australian and New Zealand guidance.[7, 8, 12]

Limited evidence was cited to support the key characteristics of 'droplet transmission' outlined in the literature. These include 1) exclusive short-range transmission, 2) specific large particle size involvement and 3) transmission via upper airway mucosal surface contamination. The CDC states that evidence for 'droplet transmission' comes from outbreak reports, experimental studies and aerosol dynamics information.[3] They cite four outbreak investigations[40, 42-44] and one experimental study;[41] none of which provide strong evidence to support predominant or sole droplet-based transmission. The CDC[3] also cite two aerosol dynamics studies[37, 45] neither of which supports traditional droplet transmission characteristics. In fact, one of the cited studies reported on the predominance of submicron particles within respiratory exhalations.[45] The CDC[3] outline that there is evidence of the nasal mucosa and conjunctiva being susceptible portals of entry for respiratory viruses and cite a study where subjects were artificially inoculated with varying doses of RSV via their nose and eyes.[31] CDC[3] authors state that acquisition of influenza has been prevented by droplet precautions, for which a narrative review is cited[46] and further American guidance outlines that "viruses whose major mode of transmission is via droplet contact rarely have caused clusters of infections in group settings through airborne routes" although no associated citations are provided.[36]

According to extant guidance, examples of infectious agents transmitted by the droplet route include *Bordetella pertussis,*[1, 3, 5, 7, 11-13] mumps,[12, 13] parainfluenza,[2, 12] adenovirus,[2, 3, 5, 12] rhinovirus,[3, 5, 12] *Mycoplasma pneumoniae*,[3] Group A *streptococcus*,[3, 5, 11, 13] norovirus,[7] RSV,[2, 12] *Neisseria meningitides*,[1, 3, 5, 7, 13, 35] avian influenza A(H5N1),[2] rubella,[1, 11-13] SARS CoV-2,[8] SARS-CoV,[2, 3] *Corynebacterium diphtheriae*,[1, 13] *Yersinia pestis*,[1] 'the common cold'[8] and influenza virus[2, 3, 5, 7, 8, 11-13, 35] with later WHO guidance specifying seasonal influenza.[1]

3.4 What is the current definition of airborne transmission?

Fourteen pieces of organisational expert opinion were included for this research question. Alongside two pieces of guidance from the World Health Organization[1, 2] other SIGN50 level 4 guidance was considered from seven countries; the U.S.A,[3, 5, 36] Australia,[6, 7] New Zealand,[8, 47] England,[9, 10] Ireland,[35] Canada[12] and Hong Kong.[11]

IPC guidance from around the world outlines that airborne transmission involves the inhalation of infectious 'small' aerosol particles (or 'droplet nuclei') which have been generated by the respiratory activities of an infectious host.[1-3, 5-9, 11, 12, 35, 36, 47] Guidance outlines that the particles involved in airborne transmission can be dispersed over large distances[1-3, 6, 7, 10-12, 36] and remain infective in the air for prolonged time periods, meaning that close contact is not required for transmission.[1-3, 6-9, 11, 12, 35, 36, 47] Some sources outline that the particles involved in airborne transmission are <5μm in size[3, 5, 7, 11, 36] whilst other guidance specifies that airborne transmission involves inhalation of particles down to the lower airways.[7, 10]

English and Canadian guidance emphasises that the aerosols involved in airborne spread can facilitate transmission, not only via inhalation, but by direct projection of infectious particles onto mucous membranes, at close range, however relevant citations are not provided to support this.[9, 10, 12] Guidance frequently outlines that the small particles, or aerosols which facilitate airborne transmission, can be carried on air currents and via exhaust systems.[3, 7, 11, 35, 36] The CDC[3] cites a narrative review,[48] an animal study[49] and two outbreak reports[50, 51] to support this concept. In the 1985 outbreak described by Bloch et al, a child with measles attended a paediatric

medical office resulting in seven secondary cases.[51] Only one secondary case had face to face contact with the index patient at <1m, three were never in the same room as the index patient and one arrived one hour after the index patient left.[51] Airflow studies supported the hypothesis of long-range transmission although indirect contact transmission cannot be definitively ruled out.[51] In Coronado's 1993 TB outbreak report, length of hospital stay and proximity to an infected case's room were significantly associated with infection, however, staff patterns and patient activities were not fully reported.[50]

Most guidance documents use vague descriptors to define airborne transmission such as "long distances", "smaller than droplets" and "remain infective over time".[3, 9, 10, 36] Some, however, use more specific language, with Canadian authors describing a long distance as greater than 2m[12] and WHO guidance, more than 1m.[2] Regarding particle suspension time, Public Health England (PHE) guidance simply outlines that aerosols "remain in the air for longer" than droplets[9] whilst New Zealand guidance specifies that they "can stay suspended in the air for hours"[8] and the CDC outline indefinite airborne suspension.[36]

The CDC state that 'droplet nuclei' are "the residue of evaporated droplets […] produced when a person coughs, sneezes, shouts, or sings".[3, 36] Guidance from New Zealand and Australia also includes talking and breathing in the list of respiratory activities which create 'small particle aerosols'[7, 8] whilst other Australian guidance highlight that "droplet nuclei can […] be generated through aerosol-generating procedures (AGPs), such as intubation, suctioning, bronchoscopy, or the use of nebulisers".[6] The CDC outline that droplet nuclei persist in certain favourable conditions such as cool, dry atmospheres with little to no direct sunlight exposure or sources of radiation.[36] Similarly, Australian guidance states that droplet nuclei are formed by evaporation of larger droplets in conditions of low humidity.[7]

Although most guidance appeared to use the two terms of 'droplet nuclei' and 'aerosols' interchangeably, Canadian guidance differed from other sources by distinguishing between the two. Authors outline that the motion of respiratory aerosols is governed principally by particle size, which ranges from 10-100μm, whereas droplet nuclei are described as being <10μm, with their motion controlled by "other physical parameters".[12]

Specific types of evidence are cited to support the concept that a certain pathogen causes spread of infection via airborne transmission. The CDC state that evidence of ultra-violet (UV) light efficacy in preventing influenza transmission during the pandemic of 1957-58 supported the theory of airborne influenza transmission[3] whilst Canadian guidance cite two outbreak reports where measles infection appeared to have been transmitted to vulnerable persons via the air of a room, which the index case had vacated more than one hour earlier.[12] The CDC[3] and Public Health Agency of Canada[12] identify *Mycobacterium tuberculosis* as an airborne pathogen with citation of an animal study[49] and two healthcare associated outbreak reports.[52, 53] Both reports do not provide evidence for a specific transmission mode but rather, general nosocomial acquisition of TB by patients and healthcare workers.[52, 53] Both CDC[3] and Canadian guidance[12] cite a measles outbreak report where airborne transmission from an athlete to two spectators seated 30 metres above at a sporting event is hypothesised, however, isolate matching was not conducted and failure to identify another infection source is a possibility.[54] Both the CDC[3] and Public Health Agency of Canada[12] acknowledge the airborne transmission potential of smallpox with reference to a German hospital outbreak where smallpox was transmitted to a number of patients, none of whom had direct face-to-face contact with the index case, care from shared staff, or shared patient care equipment.[55, 56] The airborne transmission hypothesis was also supported by details of specific case locations and/or activities, smoke dispersion patterns and the timings of symptom onset for infected cases.[55, 56] The CDC[3] cite a 1985 observational retrospective study where authors postulate that a difference in nosocomial acquisition rates of varicella zoster between two similar paediatric healthcare sites was attributable to the use of negative pressure isolation rooms, however the study is limited by its uncontrolled design and the paper lacks detail regarding patient population demographics and potential concurrent changes to IPC measures.[57] In another CDC[3] cited study, a hospital outbreak of varicella zoster is described where airborne transmission is hypothesised based on isolation of the index case, smoke dissemination patterns as well as a correlation between infection and proximity to the index case's room, however a hypothesis of indirect transmission via staff or equipment cannot be discounted.[58]

According to extant guidance, examples of infectious agents transmitted by the airborne route include *Mycobacterium tuberculosis,*[1, 3, 7, 8, 11, 12, 35, 36] *Aspergillus* species,[3] measles virus,[1, 3, 7, 8, 11, 12, 36] smallpox virus,[12, 36] Mpox[12] and varicella-zoster virus.[1, 3, 8, 11, 12, 36]

3.5 How are infectious agents released into the air of the health and care environment from the respiratory tract with consideration of particle size, distance and clearance/fallout time?

Sixty-four primary research studies and six organisational expert opinion pieces were included for this research question. Of the 64 research studies, 20 were from the U.S.A,[59-78] 12 were from the U.K,[79-90] seven were from Australia,[91-97] three each from Germany,[98-100] France,[101-103] and Singapore,[104-106] two each from Hong Kong,[107, 108] Uganda,[109, 110] Canada,[111, 112] South Korea[113, 114] and Sweden[115, 116] and one from each of the following countries; Italy,[117] Turkey,[118] Norway,[119] South Africa,[120] Japan[121] and the Netherlands.[122]

Of the six organisational pieces of expert opinion, two were from the UK,[9, 123] two were from the U.S.A,[3, 124] one was from the WHO[2] and one was from the Public Health Agency of Canada.[12] All were graded SIGN50 level 4.

All 64 primary studies included for this research question were observational air sampling investigations and were graded SIGN50 level 3. Researchers sampled exhaled or ambient air during participant respiratory activities and/or medical procedures to identify pathogens released into the air and/or determine the numbers and/or sizes of respiratory particles produced.

Many studies were focused on the identification of specific pathogens in the air surrounding infected subjects. Fourteen studies related to SARS-CoV-2,[59, 67, 72, 73, 104-106, 111, 114-116, 118, 119, 121] nine to influenza A and/or B,[60, 65, 74, 77, 78, 88, 90, 107, 112] four to *Mycobacterium tuberculosis,*[66, 109, 110, 120] five to *Pseudomonas aeruginosa*,[91, 92, 96, 97, 103] four to *Staphylococcus aureus,*[75, 92, 95, 103] two to *Stenotrophomonas maltophilia*[91, 92] and *Pneumocystis jirovecii* [101, 102] and one to each of the following pathogens;

respiratory syncytial virus (RSV),[83] rhinovirus,[64] measles,[70] *Burkholderia cepacia* complex,[91] coagulase negative *staphylococci*,[76] MERS-CoV [113] and *Aspergillus fumigatus.*[122] In addition, one 2019 study assessed the general nature and number of gram-negative bacteria produced by coughing cystic fibrosis patients[95] whilst another 2013 study screened participants for multiple respiratory infections such as parainfluenza, rhinovirus, RSV and influenza.[94]

Six included papers did not involve identification of an airborne pathogen but focused solely on the particle counts and/or sizes of particles produced during respiratory activities.[63, 68, 79, 98-100] Fifteen papers involved particle count and/or size measurement during medical procedures on participants.[61, 62, 69, 71, 80-82, 84-87, 89, 93, 108, 117]

All air sampling studies have inherent limitations, meaning results should be interpreted with caution, these include:

- specific environmental conditions under which samples were obtained may affect results for example temperature, humidity and air current patterns
- air samplers will not capture all produced particles or pathogenic material. Authors report a reduced collection efficiency for smaller particles, particles lost to impaction, and some provided evidence for cone-shaped collectors redirecting exhalation flows backwards away from sampling equipment
- maintaining viability of pathogens within samples is highly challenging as delicate pathogenic material can become damaged during the sampling process or deteriorate over time/during storage and/or transportation
- findings regarding the characteristics or behaviour of pathogens in the air may also be influenced by the specific strain, phase of infection at time of sampling and/or host infectivity/characteristics
- air samples taken at a distance from a human source may not be of respiratory tract origin. They may be from shed skin, linen or re-aerosolized from surfaces

- comparison of data between air sampling studies is made more challenging through use of heterogeneous air sampling equipment, laboratory techniques and presentation of results.

3.5.1 Distance

Eighteen included studies reported on the distances from infected sources where pathogens could be detected in air samples.[59, 67, 70, 72, 83, 92, 95-97, 101, 102, 104, 105, 112-114, 118, 119] Most studies involved RNA or DNA detection which does not indicate viability or infectivity. RNA or DNA was detected at distances of 1-5 metres across included studies which were heterogenous in terms of pathogen studied (including specific variant), population characteristics, procedures reported and environmental parameters.

Detection of viable exhaled pathogens at specified distances was assessed in seven studies.[59, 83, 92, 95-97, 113] Viable *Pseudomonas aeruginosa* was identified at 2m[92, 96, 97] (and 4m)[96, 97] from coughing patients with cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) and/or bronchiectasis,[92, 96, 97] viable gram-negative bacteria and *S. aureus* at 4 metres from coughing CF patients,[95] viable RSV at one metre from paediatric patients,[83] viable SARS-CoV-2 was detected at 4.8 metres from a single patient[59] and in one study, viable MERS-CoV was detected at 2-3m and 3-4m from one and two infected patients respectively.[113] Most study subjects were sampled in health and care settings with five studies conducted in controlled environments[92, 95-97, 119] and one in the community.[67] All studies had significant limitations. No studies tested staff, visitors and/or parents who may have contributed to samples and none provided adequate detail on medical procedures undergone by subjects. Confidence regarding subjects maintaining distances to the sampler was only associated with eight[70, 83, 92, 95-97, 113, 119] of 18 studies, three of which were specific to patients colonised with *P.aeruginosa*.[92, 95, 97] There was a frequent lack of detail concerning environmental factors which could affect distances travelled by viable particles/pathogens, for example air currents, temperature and humidity. Only four studies provided vague detail regarding source activities for example talking and/or symptoms experienced during sampling for example ‘mildly symptomatic’.[67, 70, 113, 119] General limitations include an inability to determine if captured particles originated from the subject’s respiratory tract, skin, clothes or environment and

regarding infectious dose, it is unclear if exposure at distances associated with detection would lead to infection.

Based on the limited evidence the following conclusions can be drawn; SARS-CoV-2 RNA is likely detectable at 2-4m from infected subjects,[67, 72, 119] viable MERS-CoV may be detectable at 2-3m from infected subjects,[113] viable *Pseudomonas aeruginosa*, *S. aureus* and strains of gram-negative bacteria can be identified at 4m from coughing patients with cystic fibrosis (CF),[95, 97] viable *P. aeruginosa* can be detected at 4m from patients with COPD and/or bronchiectasis[96] and viable *S. maltophilia* can be detected at 2m from coughing CF patients.[92] Further detail on these included studies is provided in the discussion below.

Kulkarni et al demonstrated that viable RSV virus could be detected in the air, one metre from 17 of 18 infected, hospitalised paediatric patients (mean age 47 weeks) and all 17 had positive samples detected in small particles (<4.7µm). Based on the age of the study cohort, maintenance of distance to sampler is assumed. Authors outlined that three of the 17 patients were ventilated, with associated open suctioning, and six were receiving oxygen via nasal cannula.[83]

In a 2019 Canadian study, investigators sampled the air at “2.1-2.5 metres” from 16 hospitalised adults infected with influenza. Four were infected with influenza A (H3N2), nine with influenza A (H1N1) and three with influenza B virus. Patients were situated in single rooms of an acute teaching hospital with air change rates of 4-6 per hour. Influenza A RNA was detected in air samples associated with six of 13 influenza A infected patients and for two patients at 2.1-2.5 metres in particles <1µm in size. There were no significant associations identified between air sample positivity and influenza virus type, admission to ICU or need for oxygen therapy, although the study was likely underpowered. The paper does not outline how many days from symptom onset patients were when sampling took place. One patient was reported to require mechanical ventilation and nine required oxygen therapy, it is unclear if this was ongoing during sampling and whether this applied to the positive sample cases.[112]

Bischoff et al’s 2016 observational study of a single patient with measles was carried out in a negative pressure isolation room at a tertiary hospital in the U.S.A. Air was

sampled at day 5 post rash onset (18 days post-exposure) when the patient had "minor coughing episodes". The study detected measles virus RNA in particles smaller than 4.7µm, at 1.21 and 2.43 metres from the patient's head. In contrast to many other studies, the study's findings were strengthened by monitoring of the subject's symptoms and movements during sampling (the patient was sitting up in bed during sampling).[70]

Seven included studies presented findings on SARS-CoV-2 RNA detection at specified distances from source (1 to 4.8m)[67, 72, 104, 105, 114, 118, 119] with only one reporting on the presence of viable SARS-CoV-2 virus.[59]

In Lednicky et al's 2020 study, low amounts of viable SARS-CoV-2 virus (16-44 GE/L of air) were detectable in the air at distances of up to 4.8 metres from infected hospitalised patients using 2 active air samplers. Air samples and patient nasopharyngeal swab viral isolates were compared via genomic sequencing, indicating that "the same consensus genome sequence was present in the virions that had been collected in all the air samplings. Moreover, they were an exact match with the corresponding sequences of the virus isolated from patient 1".[59] Aside from reliance on the use of partial genome sequences for matching, there is a significant barrier to these findings providing confirmation of source. During the COVID-19 pandemic, SARS-CoV-2 variants swept through populations quickly resulting in little temporal genomic variation in circulating virus, therefore, a partial or identical genomic sequence match, cannot definitively rule out alternative sources such as other patients, health care workers or visitors.[59] Further evidence is required to confirm the distance of detection of viable SARS-CoV-2 from source.

Three studies detected SARS-CoV-2 RNA beyond two metres. One Turkish dental study involved detection of SARS-CoV-2 RNA at 2.53 and 3.1 metres from five of 24 patients' heads following ten minutes of ultrasonic scaling and five minutes of non-contact tooth drilling, however the influence of dental procedural elements on pathogenic spread must be considered.[118] Another 2022 Norwegian study detected SARS-CoV-2 RNA in air at two metres from infected subjects who were mildly symptomatic, following 15 minutes of talking.[119] RNA was also detectable at four metres from an area that hosted eight of the 12 infected subjects for approximately two hours and 40 minutes (48,000L of air sampled).[119] Both sets of findings are

associated with reasonable confidence regarding maintenance of distance to samplers.[119] In a small 2022 community-based study, SARS-CoV-2 RNA was detected at 1.8m and 2.2m from two mildly symptomatic COVID-19 infected individuals based on 180 minutes of sampling (540L of air) and 90 minutes of sampling (270L of air) respectively.[67] Both Chia and Ong et al identified SARS-CoV-2 RNA at one metre distances from patients housed in airborne isolation rooms[104, 105] and in a 2020 USA study, three of 13 hospitalised COVID-19 patients had associated SARS-CoV-2 RNA positive air sample results following collection of 840L of air.[72] One positive sample was obtained at a 1.4 metre distance and the other two at 2.2 metres. No RNA was detected at distances of 3.2 metres.[72] In a 2020 study by Kim et al, all 52 air samples collected at a 2m distance from eight hospitalised COVID-19 patients was negative. Sampling was conducted at admission, and at three, five and seven days later.[114] Current limited evidence indicates that SARS-CoV-2 RNA can be detected at distances greater than two metres from infected subjects but due to small sample sizes and lack of reporting detail, it is unclear whether this is common and/or heavily reliant on circumstantial factors such as air currents, source symptoms etc. Detection of viral RNA is not a confirmation of viability or infectivity.

In a 2016 South Korean study, viable MERS-CoV virus was detected in air samples collected 3-4m away from two infected patients (patients 1 and 2) in one hospital and 2-3m away from one patient in another hospital (patient 3).[113] All patients were in the late stages of infection (16-22 days post symptom onset) and maintenance of distance to sampler was likely for patient 3 who was bed-bound. Both patients 1 and 2 were receiving mechanical ventilation during the sampling period which was also conducted 30-60 minutes post endotracheal suctioning. Patient 3 was not receiving mechanical ventilation, but their last positive PCR test was conducted 6 days prior to sampling.[113]

A 2019 study by Stockwell et al. detected viable *P. aeruginosa* aerosol samples following five minutes of coughing by 12 patients with either COPD or bronchiectasis and positive *Pseudomonas aeruginosa* sputum samples. Five aerosol samples were positive at 2 metres and four at 4 metres. Total mean aerosol counts were low (two colony forming units (CFU) at two metres and three CFU at four metres).[96] Viable

P. aeruginosa was also detected in five-minute cough aerosol samples in two Australian studies involving cystic fibrosis patients with chronic *P. aeruginosa* infection at distances of two and four metres respectively.[92, 97] In one of these studies, for three individuals with *Stenotrophomonas maltophilia* in their sputum, *S. maltophilia* was also cultured from their cough aerosol samples at two metres.[92] In the other, *P. aeruginosa* CFU counts significantly decreased with increasing distance (p=0.001).[97]

In another study by Wood et al. the positive sputum samples and cough aerosol samples of cystic fibrosis patients with either a history of *S. aureus* respiratory infection (n=16) or history of GNB respiratory infection (n=15) were studied. Eleven out of 18 GNB organisms and eight of 16 *S. aureus* organisms were cultured at four metres.[95]

Choukri et al detected *Pneumocystis jirovecii* DNA at one, three and five metres from hospitalised *Pneumocystis* pneumonia patients (n=15). Twelve had HIV and nine had received treatment one to nine days before air sampling took place. There was a significant decrease in fungal concentrations of samples collected at one metre and those collected at five metres (p= <0.05).[101] In another *P. jirovecii* detection study, three of 17 hospitalised, immunocompromised patients diagnosed with pulmonary colonisation had positive DNA air samples detected at one metre but no positive samples at five metres. For both studies, samples at five metres were taken at patient room entrances where contributions to samples from other sources cannot be ruled out.[102] These studies suggest that *P. jirovecii* DNA may be detectable at 3-5m from source, however, these findings are specific to certain groups of immunocompromised patients.

3.5.2 Particle size without assessment of pathogen presence

Six papers described the size of particles generated during respiratory activities by non-infected individuals[62, 63, 79, 82, 99, 100] with two assessing the generic particle production of those with respiratory infections.[64, 107] Studies suggested that; a significant proportion of particles produced at source when breathing are <5µm in size, whether healthy[99, 100] or infected with influenza[107] or human rhinovirus.[64] The

majority of particles being <5μm in size were also seen when singing, speaking or shouting activities were performed by healthy subjects.[99, 100] In line with the above findings, further studies showed that when speaking or coughing, the mean diameter of particles produced near to source (5-20cm) was close to 1μm, however these studies were specific to healthy cohorts and had small sample sizes.[62, 63, 82] Further information on included studies is provided in the discussion below.

Breathing

At five centimetres from source, ten healthy participants produced a median mean particle diameter of 1.48μm (IQR 1.22-1.54) for normal breathing and 1.00μm for deep breathing (IQR 0.98-1.14).[62] These data were attained using an aerodynamic particle spectrometer (APS) which could measure particles between 0.53-20μm in size.[62] Fabian et al assessed the particle counts and particle sizes exhaled by ten influenza infected patients at source, during five minutes of tidal breathing. Based on equipment which captured data on particles of size 0.3-5μm, approximately 70% of the particles measured were 0.3-0.5 μm in size, 17% were 0.5-1 μm and 13% were between 1 and 5 μm.[107] As part of a 2011 study, 17 university students with human rhinovirus infection breathed normally into a mouthpiece for three minutes. The air sampler collected size fractionated samples from 0.3 to 10μm and 82% of exhaled particles were found to be in the 0.3–0.49μm size range.[64] These studies suggest that a significant proportion of particles produced at source when breathing are <5μm in size.

Speaking

At five centimetres from source, ten healthy participants produced a median mean particle diameter of 1.28μm (IQR 1.14-1.43) when talking.[62] An aerodynamic particle spectrometer (APS) measured particles from 0.53-20μm in size.[62] A similar study found that particle size distribution appeared to be independent of language spoken or loudness with the “mean particle diameter remaining near 1μm” whilst vocalising the letter ‘a’ or voicing the ‘rainbow passage’, however, no statistical analysis results are presented.[63] An aerodynamic particle spectrometer (APS) measured particles produced in the range of 0.5-20μm in size and participants were approximately

7.5cm from the sampler.[63] In these study cohorts (healthy persons) the mean particle diameter of particles produced near to source when speaking, was close to 1µm.

Coughing

At five centimetres from source, ten healthy participants produced a median mean particle diameter of 1.03µm (0.94-1.46) when performing forced coughing. An APS was used which measured particles in the 0.53-20µm size range.[62] In Shrimpton et al's 2022[b] study, particle concentrations during three volitional coughs of 11 adults without respiratory infection were recorded at 20cm from source.[82] The majority (86.5%) of cough associated particles were <1µm diameter. An optical particle sizer was used which measured particle sizes in the 0.3 -10µm size range.[82] Similar to the data associated with speaking, a mean particle diameter of 1 µm was demonstrated in these cohorts (healthy participants) during coughing.

Comparison of respiratory activities

Murbe et al's 2021 study examined particle size distribution patterns (0.3-25µm) for differing respiratory activities performed by adult professional singers. Murbe et al found that particle size distribution did not appear to change based on respiratory activity (speaking, singing or breathing).[99] In slight contrast to this finding, Gregson et al (2021) found that amongst 25 professional singers, size distributions for speaking, singing and breathing were generally similar, but with speaking and singing on average generating larger particles than breathing.[79]

Murbe et al (2021) found that the majority of particle sizes (>99%) at 0.81m from the subject when breathing, speaking or singing, were <5µm in size.[99] Similar findings were presented in another paper by Murbe et al where around 99% of particles (between 0.3 and 25µm) emitted during speaking, singing or shouting by adolescent singers were found to be <5µm in size at 0.81m from source.[100] Due to small sample sizes (n=8 for both) these studies are likely underpowered, and more research is needed to support findings.

3.5.3 Particle size including assessment of pathogen presence

Twenty-three papers presented data on the sizes of respiratory particles found to contain or carry viral or bacterial material.[65-67, 70, 72-75, 77, 83, 88, 91, 92, 94, 95, 97, 104-106, 109, 112, 115, 116] Most reported on particle sizes associated with viral RNA or DNA[65, 67, 70, 72, 88, 94, 104-106, 112, 115, 116] rather than those associated with viable, potentially infectious pathogens[66, 73, 75, 91, 92, 95, 97, 109] whilst three studies reported on both.[65, 74, 77] Eleven studies were highly controlled with collection of samples at, or very close to, source using a sampler with cone collector or mouthpiece attachment.[65, 66, 74, 77, 91, 94, 95, 106, 109, 115, 116] Air samples were taken at a specified distance from the source in 12 studies[67, 70, 72, 73, 75, 83, 88, 92, 97, 104, 105, 112] and only in four was maintenance of distance to the sampler confirmed[92, 97] or assumed to be highly likely.[75, 83] Studies provided insufficient detail regarding a multitude of aspects which may influence particle size. No studies, where it was applicable, reported on testing of staff, parents or visitors, who may have been present and contributed to air samples. Commonly missing information included medical procedures undergone by participants during sampling periods, symptoms experienced by participants, whether distances to air samplers were maintained, participant activities during sampling such as sneezing or talking and environmental conditions, for example, temperature or humidity. Based on current evidence the following conclusions can be drawn; viable influenza virus, influenza RNA and SARS-CoV-2 RNA is detectable in respiratory exhalations at close range (≤1m), and in particles <5μm.[74, 77, 104-106, 115, 116] Viable SARS-CoV-2 virus, SARS-CoV-2 RNA and influenza A RNA is detectable in airborne particles <1μm in size but evidence for associated distances from the source itself cannot be definitively established.[67, 73, 88, 112, 115] *P. aeruginosa* is detectable in coughing exhalations in particles <5μm diameter both at source, at 2m and 4m.[91, 92, 97] Small particles (<5μm) may carry the majority of; aerosolised Influenza RNA viral load within 1m of source,[65, 77] culturable *P. aeruginosa* from coughing exhalations both at source and at a 2m distance[91, 92] and culturable TB from coughing exhalations at source, however, further research is needed.[66, 109] TB findings, however, were specific to patients with acid fast bacilli (AFB) smear sputum positivity and an unknown immunocompetency and/or treatment status.[66, 109] Further detail on these included studies is discussed below.

Respiratory syncytial virus

In a 2016 UK study, viable RSV virus was detected 1m away from 17 infected, hospitalised, paediatric patients within particles as small as 0.65-1.1µm and 65% of total plaque forming units (PFU) per/L of air was in the <4.7µm particle size range.[83] Authors outlined that three of the 18 patients were ventilated, with associated open suctioning, and seven were receiving oxygen via nasal cannula. Based on the age of the study cohort, maintenance of distance to sampler is assumed.[83]

Influenza

Three papers reported on viable influenza virus detection[65, 74, 77] and five presented influenza RNA findings.[65, 74, 77, 88, 112] In a 2018 observational study, viable influenza virus was detected in 52 fine aerosol (0.05-5µm) mixed breath and speech exhalation samples at close range (cone sample collection) from volunteers (n=142, age 19-21 years, all infected with influenza). It is unclear, however, how many subjects were associated with the 52 positive samples.[74] In a separate study, viable influenza was detected at close range (cone sample collection), in small particle size samples (<5µm) from two of 37 influenza participants but this was during mixed breathing and coughing rather than mixed breathing and speaking.[77] In another study, viable influenza was detected at source in cough exhalation samples from two of 21 influenza infected students.[65]

Air surrounding influenza patients (n=3) was sampled in a 2016 UK study. Influenza RNA was detected at 1-2 metres in particles of <1µm (n=1), 1-4µm (n=3) and >4µm (n=1).[88] In another study involving 16 hospitalised influenza patients (n=4 influenza A H3N2, n=9 influenza A H1N1, n=3 influenza B), air was sampled at distances of '0.5-1' (<1m) and '2.1-2.5 metres' (>2m) from source.[112] Six patients produced positive influenza A RNA air samples in all particle size ranges (<1µm, 1-4µm and >4µm) and at both '0.5-1' metre and '2.1-2.5' metre distances from source.[112] In Milton et al's 2013 study, samples were collected at close range (cone sample collection) to 37 influenza patients during breathing and coughing, and viral RNA was detected in both coarse (>5µm) and fine (<5µm) particle samples for 16 and 34 participants respectively.[77] Influenza RNA was detected in 166 fine (0.05-5µm) and 88 coarse (>5µm) aerosol samples at close range (cone sample collection) from a study

involving 142 volunteers. It is unclear, however, how many subjects were associated with the 166 and 88 positive samples respectively.[74]

Lindsley et al (2010) reported that based on positive samples from 32 infected patients, 65% of total influenza viral RNA, identified at source, was in size fractionated samples of <4µm in diameter.[65] Similarly, Milton et al's 2013 study reported that fine fraction (<5µm) samples (n=34) contained, on average 8.8-fold [CI 4.1 to 19] more viral RNA copies than coarse fraction (>5µm) particle samples at <1m from source (n=16).[77] These studies, however, have significant limitations and further research is needed to explore the relationship between particle size and viral material content.

SARS-CoV-2 Virus

Seven studies assessed SARS-CoV-2 RNA in particle size fractionated air samples[67, 72, 104-106, 115, 116] and one study provided particle size findings related to viable SARS-CoV-2 virus.[73]

Viable SARS-CoV-2 virus was detected in particles <1µm in size, in the vicinity of one of six COVID-19 patients where 105 litres of air was collected over a 30-minute period at "the foot of each patient's bed".[73]

Two studies reported that SARS-CoV-2 viral RNA could be detected at 2.2m from source, in particles smaller than 4µm,[67, 72] both studies reported on subject symptoms but were associated with only one positive case each. Two hospital-based studies reported SARS-CoV-2 RNA detection at 1m from source, in particles smaller than 4µm for six and two COVID-19 infected patients respectively.[104, 105] In both studies, authors specified that no patients received supplementary oxygen or underwent AGPs 24 hrs prior to sampling, however a list of procedures considered to be AGPs is not provided. In the study with two positive cases, both had cough symptoms.[104]

SARS-CoV-2 RNA was detected in particles <5µm, at close range (via cone sample or mouthpiece collection) to infected participants.[106, 115, 116] One of these studies found, based on 13 participants with RNA positive exhalation samples, that particles <5µm in size constituted 85% of the total aerosol viral load.[106] This study, however,

had significant limitations and further research is needed to explore the relationship between particle size and viral material content.

Mycobacterium tuberculosis

Two studies reported on the particle sizes associated with air samples containing culturable TB.[66, 109] Fennelly et al used an Andersen cascade impactor to collect air samples from 101 TB patients over five minutes of forced coughing at source. 28 positive samples were collected in six size fractionated samples from 0.65 to >7µm. Authors reported that 96.4% of culturable particles were in the size range 0.65-4.7 µm, with most falling within 1.1-2µm.[109] These findings were similar to those from an earlier TB study where the majority (90%) of culturable TB particles were collected within size fractionated samples (0.65-3.3 µm) from four TB patients.[66]

Pseudomonas aeruginosa

Particle size and *P. aeruginosa* was assessed in three studies.[91, 92, 97] Viable *P. aeruginosa* was detected in small particles (<3.3µm) at one, two and four metres from source in Knibbs et al's 2014 study.[97] Two studies reported that the majority of culturable *P. aeruginosa* particles (approx. 70%) collected from cystic fibrosis patients at two metres or source respectively, were <4.7µm and <3.3µm in size, respectively.[91, 92]

Other pathogens

Further particle size air sampling studies involved detection of *S. aureus,*[75, 95] gram-negative bacteria,[95] parainfluenza,[94] rhinovirus,[94] and measles virus.[70]

An Australian 2013 study showed that viral parainfluenza and rhinovirus RNA could be detected within small particle size fractionated samples (0.65-1.1µm) from infected persons at source following 10 minutes of breathing or 10 forced coughs although it was unclear from reporting how many participants this applied to.[94] Bischoff et al's 2016 observational study was carried out in a single negative pressure isolation room with "turbulent air flows" (6ACH), at a tertiary hospital in the U.S.A. The study was limited by its sample size, only reporting on 1 patient with measles. Air was sampled days 5-7 post rash onset (18-20 days post-exposure).

The study detected viral RNA in particles smaller than 4.7µm at 1.21 and 2.43 metres from the patient's head on days 5 and 7 post rash onset when the patient was experiencing mild to moderate coughing episodes.[70] In a study involving 16 CF patients with a history of *S. aureus* respiratory infection and 15 with a history of gram-negative bacteria (GNB) respiratory infection, both groups had positive sputum samples on the day of the study's cough aerosol sampling procedure.[95] Following two minutes of coughing by CF patients into a sampling rig, via a mouthpiece, the mean percentage of total bacteria cultured in <4.7µm particle size samples was 66.5% (SD 26.1) for the GNB organism group and 58.2% (SD 26.0) for the *S. aureus* group (p=0.46). This study suggests that viable *S. aureus* bacteria and certain strains of viable gram-negative bacteria, from the cough aerosols of colonised/infected CF patients, may exist largely within particles of <5µm at source, however, further research is needed.[95] In Bischoff's 2006 study, investigators found that *Staphylococcus aureus* was disseminated into the air of an enclosed chamber ($3.1m^3$) through the breathing and sneezing of persons with *S. aureus* nasal carriage in particles of <5µm in size.[75]

Particle size - expert opinion

SIGN level 4 (expert opinion) guidance from the CDC, the Canadian PHA and ASHRAE states that during respiratory activities and medical procedures, people, regardless of infective status, release respiratory fluid particles in a range of sizes at close range.[3, 12, 124] UKHSA and ASHRAE, in line with this concept, outline that someone with a respiratory infection will release small and large pathogen carrying particles when they breathe, speak, cough or sneeze.[123] Some droplets will fall to the ground in a few seconds, others may take tens of seconds and some minutes or hours.[3, 12, 124] Canadian guidance states that "particles [which] remain aloft for minutes or hours […] can be carried by air currents over a measurable distance, including beyond the room".[12]

Guidance outlines that aerosol size is determined by a number of factors including force and pressure during generation,[2, 12] the individual,[124] the components of the aerosolised fluid,[2] associated procedures,[12] the type of respiratory activity,[124] the loudness of vocalisation,[124] presence and stage of infection,[124] initial size with degree of evaporation[2, 12, 124] and environmental conditions such as temperature,

relative humidity and airflow.[2] Only ASHRAE's position paper provided citations to support their description of factors which influence particle size. They cited findings from two air sampling papers which were excluded due to methodological limitations as part of this review.

3.5.4 Particle counts

Nine papers assessed the effects of differing respiratory activities (breathing, speaking, singing, shouting and coughing) on numbers of particles produced.[63, 68, 79, 80, 89, 91, 93, 99, 100] Three studies assessed the relationship between particle count and respiratory infection.[78, 116, 120] The evidence base supports the general concept that speaking generates more particles than breathing,[63, 93, 99] that singing or shouting produces more particles than speaking[79, 99, 100] and that coughing produces more particles than speaking.[79] Physical exertion and increasing loudness of speech also appear to have significant effects on particle count production.[63, 68, 79, 93, 99] High inter-subject variability in particle production was a frequent finding of included air sampling studies.[63, 64, 79, 99, 100, 107, 116] For example, in one study, based on breathing samples from 10 influenza infected subjects, particle counts ranged from 67 to 8,500 particles per litre of air,[107] in another study of 25 healthy adults, particle concentration per cough ranged from 0.22 to 41 particles/cm^3 (based on particles <5µm only)[79] and in a further study particle counts per cough ranged from 400 to 516,800 while subjects had an influenza infection, and 300 to 362,700 following recovery.[78] High inter-subject variability regarding particle production has significant implications for the conduct and interpretation of air sampling studies. Using subjects as their own controls is prudent, but if not possible or appropriate, large sample sizes will be required to mitigate the effect of variability amongst the study cohort. Using the findings of air sampling studies to inform IPC recommendations is made more challenging by the concept of differing persons potentially presenting differing levels of risk, not only based on the infective pathogen or the environment, but the natural particle production tendencies of the individual. One study suggested that in addition to inter-subject particle production variation, there may also be significant intrasubject variability in particle production over time.[89] Two studies suggested that there may not be direct correlation between particle count and aerosol pathogen positivity.[116, 120] Although the studies were specific to TB (symptomatic,

pre-treatment) patients and SARS-CoV-2, their findings highlight a need for further investigation into this relationship.[116, 120] Further detail on included studies is discussed below.

Breathing

Gregson et al (2022) found that, based on 15 healthy participants, nasal breathing produced significantly less aerosols than mouth breathing (p=0.008).[80] Deep breathing or 'forced expirations' as described in Wilson et al's 2021 study increased particle counts 227.6 fold when compared to tidal breathing (p= <0.001).[93]

Both Murbe et al (2021 1336) and Asadi et al (2019) found that speech particle emission rates were significantly higher than those produced during breathing (p=<0.001 and p=<0.05 respectively).[63, 99] Similarly, Wilson's 2021 study found that, compared to quiet tidal breathing, talking increased particle counts 34.6-fold (p=<0.001).[93] The main limitations of these studies include small sample sizes, and specificity to healthy cohorts.

Speaking, singing and shouting

Three studies reported that singing generates greater particle numbers than speaking.[79, 99, 100] Murbe et al reported that particle emission rates were significantly higher for singing compared to speaking, increasing by a factor of 16.2 (p=<0.001).[99] Similarly, Gregson et al reported that singing generated approximately 1.5 to 2.5 times more particles than speaking in their cohort (p= <0.00001).[79] Another study by Murbe et al further supported the findings associated with singing and presented additional findings on shouting. Based on a small group of adolescents (n=8) singing and shouting both appeared to produce significantly more particles than speaking (5.87 and 36.22-fold increases respectively, both p=<0.001).[100] Similarly, Wilson's 2021 study found that, compared to quiet tidal breathing, shouting increased particle counts 163.6-fold (p=<0.001).[93] The main limitations of these studies include small sample sizes, and specificity to healthy cohorts.

Coughing

Three studies found that coughing produced significantly more particles than breathing.[82, 91, 93] Wainwright et al compared the mean total particle counts of forced coughing versus tidal breathing for seven CF patients. Mean particle counts were significantly lower during tidal breathing (2 [C.I -0.5 to 15]) than during voluntary coughing (85 [C.I 28 to 238] p= 0.001).[91] Similarly, Shrimpton et al found increased particle counts associated with coughing when compared to breathing. Particle concentrations during three volitional coughs of 11 adults without respiratory infection were recorded. A median peak aerosol concentration of 1260 particles/l (IQR 800-3242 [range= 100-3682]) was recorded. This was compared to tidal breathing which generated a median particle concentration of 191 particles/l (IQR 77-486 [range= 3.8-1313]).[82] Wilson's 2021 study which involved particle count measurement for 10 healthy subjects found that coughing increased particle counts 370.8-fold compared to quiet tidal breathing (p=<0.001).[93] Gregson et al's 2021 study involving 25 adult professional singers found that coughing produced more particles (8.6 times more) than speaking at a moderate volume (70-80dB).[79]

Exercise

Sajgalik et al identified a significant increase in particle counts generated by eight middle-aged healthy volunteers when performing exercise.[68] There was a significant increase in particle counts, in both size fractionated categories (0.3-1 and 1-5μm) compared with breathing at rest, when exercising at 50%, 75% and 100% of age predicted heart rate reserve (HRR) (p= <0.05).[68] Following 20 minutes of exercise, with participants reaching a mean peak heart rate peak of 173 beats/min (+/- 17) and mean maximal minute volume of ventilation 120L/min (+/- 23), particle concentrations in the 0.3-1μm and 1-5μm size fractionated samples increased by an approximate factor of 31 and 17 respectively.[68] Wilson et al also identified a significant increase in particle counts with exercise. Based on a one-minute sampling period, pedalling to achieve ~70% of maximal estimated HR increased particle counts 58-fold compared to quiet tidal breathing (p=<0.001).[93]

Volume of speaking/singing

Asadi et al reported, based on 10 young, healthy participants, that there was a positive correlation between speech volume and particle emission rate (Correlation coefficient 0.865, $p=6.8x10^{-10}$).[63] Speaking loudly resulted in a 10-fold higher emission rate on average compared to speaking the same series of words quietly.[63] Similarly, Murbe et al's 2021 study suggested that as volume increases so does particle emission rate. When transitioning from piano to mezzo-forte, particle emission rate increased by a factor of 6.3 (p=<0.001) whilst a transition from mezzo-forte to forte was associated with a 2.8 factor increase (p=<0.001).[99] In addition, Murbe et al found, that for their small cohort of adolescents (n=8), there was a weak positive correlation between sound volume and particle emission rates (r^2= 0.27, p=<0.001).[100] Gregson et al's 2021 study's findings suggested that at the quietest volume (50–60 dBA), neither singing (p= 0.19) nor speaking (p= 0.20) was significantly different in numbers of particles produced compared to breathing.[79] Median particle number concentration for both singing and speaking increased by a factor of 10–13 as loudness increased from 50–60 decibels (dBA) to 90–100 dBA. This was mirrored in median particle mass concentration results where approximate 20-fold increases were seen (p=<0.001).[79] These four studies have very small sample sizes therefore further research is needed to confirm the effects of volume on particle emission.

These findings are reflected in guidance where ASHRAE authors outline that "speaking loudly, singing, and deeper breathing associated with physical activity […] increase the number [of] … aerosols discharged into the air"[124] whilst in UKHSA's 2021 ventilation guidance, authors state that "the risk of airborne transmission is increased when occupants in an enclosed space are participating in energetic activity, such as exercising, or when they are shouting, singing or talking loudly".[123]

Inter-subject variability

High inter-subject variability in particle production was a frequent finding of included air sampling studies. Fabian et al assessed the particle counts exhaled in the breath of 10 influenza infected patients, during tidal breathing. Wide inter-subject variability was noted with particle counts ranging from 67 to 8,500 particles per litre of air.[107]

Large inter-subject variability regarding breathing was also noted in a study involving 17 university students with rhinovirus infection.[64] Tidal breathing resulted in particle concentrations which ranged from 0.2 to 7200 particles per litre of air (mean = 32 particles per litre). Four subjects were considered to be high particle producers (>500 particles/L of air).[64] Mean particle concentration for high particle producers was 3500 particles/L of air compared to 7.4 particles/L of air for low particle producers. Minute ventilation, maximum airflow during exhalation and % of predicted forced expiratory volume in 1 second (FEV1), were significantly associated with high particle production (all p=<0.05) which suggests that particle production may be associated with an individual's specific inhalational volumes and expiratory airflow.[64] In Asadi et al's study, particle emission rates whilst speaking ranged from 1 to 14 particles per second, with an average of approximately 4 particles per second.[63] Half of participants emitted fewer than 3 particles per second, but a small number (8 out of 40) emitted considerably more (exceeding the group mean by one or more standard deviations). Authors report that when vocalising an 'a' sound, "15% of the participants emitted 32% of the total particles" and when "reading aloud in English, 12.5% of the participants emitted 40% of the total particles".[63] The main limitations of Asadi et al's study included small sample sizes, with individual experiments involving only 10-30 participants and specificity to a young (18-45yo), healthy cohort.[63] In Gregson et al's 2021 study, which involved 25 adult professional singers, there appeared to be specific individuals who produced higher numbers of particles during speech compared to others.[79] Particle concentration ranged from 0.060-0.75 particles/cm^3 when speaking at a moderate volume (70-80dB).[79] Large inter-subject variation in particle emission rates was also reported when singing. Median singing particle emission rates ranged from 753 to 6093 particles/sec in one study which involved eight professional singers[99] and from 141 to 1240 particles/sec in a study with eight adolescent participants.[100] In Viklund et al's 2022 study, two of 25 participants produced a very high number of particles during coughing compared to other subjects.[116] Particle size assessment demonstrated that this increase was largely attributable to particles of size 0.4-1.1µm. Overall, particle numbers per cough ranged from 0.9 to 217.4 for their cohort of COVID-19 infected individuals.[116] Gregson et al's 2021 study also identified wide inter-subject variability for cough results.[79] In their study which involved 25 adult professional singers, particle concentration per cough ranged from 0.22 to 41 particles/cm^3 based on particles

sized <5µm only.[79] Lindsley et al's 2012 study findings reinforced the concept of high inter-subject variability in particle production.[78] Particle counts per cough ranged from 400 to 516,800 while subjects had an influenza infection, and 300 to 362,700 following recovery, this was based on particles sized 0.35-10µm.[78]

The concept of significant inter-subject variability in particle production is reflected in ASHRAE guidance which outlines that particle number and speed will "vary widely by individual, type of respiratory activity and/or metabolic intensity, the volume of vocalization, and stage of disease if the person is infected".[124]

Intra-subject variability

Hamilton et al's 2022 study findings suggested that in addition to inter-subject particle production variation there may also be significant intrasubject variability in particle production over time.[89] Breathing, speaking and coughing measurements were taken 1 month apart for six healthy adult subjects. Breathing measurements showed a moderate correlation (r=0.81) but this was not the case for speaking or coughing measurements (r=0.17 and r=0.38 respectively).[89] In contrast to this finding, Lindsley et al (2012) reported that median particle counts per cough did not significantly change between samples obtained from subjects during influenza infection and post recovery approximately two weeks later (p=0.1042).[78] However, conclusions cannot be drawn based on these small sample size studies and further research is needed.

Particle counts and viral/bacterial load of aerosols

Dinkele et al presents the concept that particle numbers generated during forced coughing, breathing and forced vital capacity (FVC) manoeuvres of TB infected patients, may not correlate with Mtb bacilli production.[120] Tidal breathing produced significantly less Mtb bacilli per breath compared to a single FVC manoeuvre or cough (2.6 fold higher (p=0.009) and 3.2-fold (p=0.00185) respectively), however, the average number of MTB bacilli per particle was lower for a single cough (0.3 fold change p= 0.009) or FVC manoeuvre (0.09 fold change p= 0.00185) than a single breath.[120] There was nil or poor correlation between particle count and Mtb bacilli count for a single cough (r^2=0.04, p=0.4), breath (r^2= 0.15, p=0.08) or FVC manoeuvre (r^2=0, p=1). Breathing is a constant activity compared to coughing which

is sporadic.[120] Within this study cohort, one minute of tidal breathing generated more bacilli than a single cough or FVC manoeuvre and following 5 minutes of sampling, all three manoeuvres returned similar rates of positivity (65-70%) for Mtb (15 coughs/15 FVC manoeuvres/5 minutes of tidal breathing).[120]

Similar findings regarding the relationship between particle and pathogen counts were reported for a cohort of COVID-19 individuals, where there was no significant association between number of exhaled particles (<5µm) and either SARS-CoV-2 RNA aerosol sample positivity or aerosol viral load.[116] Subjects with COVID-19 (n=25) appeared to exhale less particles than healthy controls (n=11) during normal breathing and airway opening breaths (p= 0.008 and 0.001 respectively), but not during coughing (p= 0.151).[116]

3.5.5 Viability of pathogens in air samples

The following viable pathogens were detected at a distance (range 1-4.8m) from infected patients; respiratory syncytial virus,[83] *P. aeruginosa,*[92, 96, 103] *Stenotrophomonas maltophilia,*[92] SARS-CoV-2,[59, 73] *S.aureus,*[75, 103] MERS-CoV,[113] and coagulase negative *staphylococci*.[76] Evidence regarding matching clinical and air sample isolates was presented for *P. aeruginosa*,[103] SARS-CoV-2,[73] and *S. aureus.*[103]

The following viable pathogens were detected at very close range (within 1m) to infected source e.g. using a cone shaped sampler inlet; *P. aeruginosa,*[122] *S. aureus,*[122] influenza,[74, 77] *Aspergillus fumigatus,*[122] and *M. tuberculosis.*[120] Evidence regarding matching clinical and air sample isolates was presented for *Aspergillus fumigatus.*[122]

The following viable pathogens were detected in respiratory emissions at source for example using air sampling equipment with a mouthpiece: *P. aeruginosa*,[91, 97] *S. maltophilia,*[91, 95] SARS-CoV-2,[111] *S. aureus,*[91, 95] *Burkholderia spp.,*[91, 95] *Achromobacter spp.,*[91, 95] influenza,[60, 65] and *M. tuberculosis.*[66, 109, 110]

Viability of the above pathogens was established through culturing, visualisation using electron microscopy, immunofluorescence assay and/or cell infectivity assays.

Seven studies were unsuccessful in their attempts to detect viable virus or bacteria in the air surrounding infected patients[70, 88] with five specifically related to SARS-CoV-2 virus.[67, 72, 105, 106, 119]

3.5.6 Procedures

This review included 15 studies which assessed particle production during the following procedures involving the respiratory tract; upper gastrointestinal (GI) endoscopy,[80, 108] upper airway suctioning,[81] manual face mask ventilation,[81, 82] intubation,[81] extubation,[81] lung function tests,[71, 84] nasal endoscopy,[61] dental procedures,[85, 117] oxygen delivery,[62, 86] high flow nasal oxygen,[62, 89, 93] non-invasive positive pressure ventilation/CPAP,[62, 86, 89, 93] chest physiotherapy,[86] nebuliser therapy,[86] supraglottic airway insertion,[87] supraglottic airway removal,[87] tonsillectomy with monopolar electrocautery[69] and myringotomy and tympanostomy tube insertion.[69] Procedures involving the respiratory tract which feature on the current Scottish AGP list but for which no studies of adequate quality were identified, are as follows; bronchoscopy, tracheotomy or tracheostomy procedures (insertion or removal), high frequency oscillatory ventilation (HFOV) and induction of sputum using nebulised saline.

None of the included procedural air sampling studies had ideal comparative baseline measurements. In order to provide true confidence that a change in particle concentration is attributable to the procedure (and not other sources for example equipment, personnel movement and/or abrasion of materials) all aspects of the procedure aside, from the entity of interest, for example intubation, should be consistent during both sampling periods. Some studies compared procedurally generated particle counts to pre-procedure baseline measurements[61, 69, 108, 117] while most elected to compare procedurally generated particle counts with respiratory activities such as breathing or coughing.[62, 71, 80-82, 84-87, 89, 93] This latter approach aims to demonstrate that some procedures may present a lower risk of respiratory infection transmission when compared to natural non-procedure associated respiratory events. Coughing events, however, were always forced thus not representing a natural process with one study providing a vague description of comparative measurements where participants were asked to perform “a series of spontaneous coughs”. Most studies were limited by their involvement of non-infected

participants only[61, 62, 71, 80-82, 85, 93, 117] and all but one by small sample sizes.[108] There was variation in how particle counts were reported with many outlining mean or median particle counts during a procedure[61, 62, 69, 71, 86, 87, 108, 117] rather than mean peak or total particle counts,[80-82, 84, 85, 89, 93] the latter two of which likely provide a greater representation of risk. The findings of some studies were strengthened by inclusion of particle size assessments,[61, 62, 69, 80, 86, 89, 93, 108, 117] however, comparisons of particle concentrations alone were common with no assessment of how particle size distributions may have changed.[71, 81, 82, 84, 85, 87] Without particle size assessment, an absence of change to average particle counts may not represent an absence of risk - the size profile of particles may have changed, with, for example, no change in particle counts but an increased proportion of smaller particles when compared to baseline measurements. Some studies were conducted in uncontrolled environments where air change rates and natural background particle counts may have been high – this could disrupt detection of particle count/size changes.[61, 86, 108, 117] Particle production does not necessarily correlate with number of infective particles and thus may not serve as an appropriate measurable proxy for risk of transmission.

Based on the limited evidence base, upper GI endoscopy, specifically procedurally induced coughs, appear to increase small particle (<10µm) production.[80, 108] Manual face mask ventilation does not appear to produce higher peak particle counts than forced coughing, although changes in particle size distribution were not assessed.[81, 82] Dental hand scaling, routine extractions and 3in1 use (water only) does not appear to significantly contaminate the air, above background particle count levels.[85] Procedures such as drilling (high speed/slow speed/surgical), 3in1 use (with air) and ultrasonic scaling appear to generate particle counts higher than baseline peak forced patient cough measurements, however the source of these particles is unknown (for instance instrumental irrigant or respiratory tract fluid).[85, 117] Non-invasive positive pressure ventilation (NIPPV) or continuous positive airway pressure (CPAP) with use of an exhalation filter, seems to produce more particles than breathing but less than forced coughing.[62, 86, 93] Breathing with oxygen delivery of up to 15L/min via a face mask does not appear to produce more particles than forced coughing.[62, 86] High flow nasal oxygen (HFNO) at flow rates of 20 and 40L/min do not appear to produce significantly more particles than tidal breathing.[62, 93] HFNO at

60L/min appears to be associated with increased particle production when compared to tidal breathing but is likely less than coughing particle production.[89, 93] Due to limited[61, 69, 71, 81, 84, 86, 87] or contradictory evidence,[61, 81, 108] conclusions cannot currently be drawn regarding upper airway suctioning, nasal endoscopy, tracheal intubation/extubation, lung function tests, chest physiotherapy, administration of nebulised saline, supraglottic airway insertion/removal, myringotomy and tympanostomy tube insertion or tonsillectomy with monopolar electrocautery. Further detail on included studies is discussed below.

Upper GI endoscopy

Two studies were included that assessed upper GI endoscopy.[80, 108] Gregson et al's 2022 study involved a particle count production comparison between tidal breathing as well as volitional and Oesophago-Gastro-Duodenoscopy (OGD) evoked procedural coughs. In this cohort (n=9 healthy participants), evoked coughing during conscious OGD generated significantly more total aerosols (in the 0.3-10μm size range) than volitional coughing, both in particle number (p=0.008) and mass (p=0.008) and created significantly higher peaks (p=0.008).[80] Based on 15 participants, conscious OGD without coughing events, did not generate more aerosols (0.3-10μm) than mouth breathing (p=0.17). Overall, the authors surmised, based on continuous air sampling results and event time stamps, that the procedural origin of particles during an OGD is likely induced coughing rather than scope insertion or removal.[80] The main limitations of this study include the small sample sizes, the involvement of forced coughing which may not mirror natural processes and unclear reporting on consistency of personnel present and activities conducted during procedural and comparator cough sampling. The small sample size limitation is particularly significant when considering the large inter-subject variation in particle production and corresponding high standard deviation (SD) values for example the mean peak particle concentration of OGD evoked coughs was 11,710L^{-1} (SD = 13,700).[80] Particle size distribution reporting is vague, but the data suggest a similar pattern of particle size distribution for evoked and volitional coughs with a large proportion of particles <5μm in size produced for both activities.[80] In a separate study that assessed particle production during 93 OGD procedures, particle counts per cubic feet of all six size fractionated samples, from 0.3 to 10μm, significantly

increased during OGD procedures (p<0.001 to <0.02).[108] Use of a dental suction device significantly reduced the number of particles sized 0.3-10µm expelled during the procedure when compared to baseline (patient in situ and breathing) (p=<0.001 to 0.046). Sedation of 34 patients (37%) appeared to have no significant effect on particle counts (p= 0.13 to 0.96).[108] This study was limited by its short baseline measurement time period and lack of information regarding staff presence and activity during sampling.[108] These studies suggest that OGD procedures increase small particle (<10µm) production, that this may be driven by procedurally associated induced coughs and that suctioning may reduce particle counts. However, further research is needed.

Upper airway suctioning

In a cohort of 19 healthy participants, mean particle counts produced (0.3-10µm size range) during upper airway suctioning, pre- and post-intubation and extubation were significantly lower than those produced during breathing (p=<0.0001-0.029).[81] The peak aerosol concentrations produced by volitional coughs and tidal breathing were many fold higher than the peak concentrations recorded during all periods of upper airway suctioning (both p= <0.0001). Although these findings contradict the concept of upper airway suctioning being considered an aerosol generating procedure, it is a small, single study with inclusion of only healthy subjects. Authors also do not report on particle size distribution; therefore, it is not possible to ascertain how particle count changes are distributed across the range of particle sizes between 0.3-10µm.[81] Chan et al's 2020 study findings similarly suggested that airway suctioning may reduce particle counts.[108] In a study which assessed particle production during 93 OGD procedures, use of a dental suction device significantly reduced the number of particles sized 0.3-10µm expelled during the procedure when compared to baseline (p=<0.001 to 0.046).[108] Murr et al, however, found in their 2021 nasal endoscopy study that a significant mean increase in particle counts was seen with use of suction when compared to pre-procedure baseline measurements (p=0.001).[61] Generally, current findings regarding particle production and upper airway suctioning are limited and contradictory.

Nasal endoscopy with and without debridement

During nasal endoscopy (with debridement) (n=19), a significant increase in mean particle counts was observed for cold instrumentation when compared with pre-procedural levels (increase of 2,462 p/ft^3 (CI 837-4,088, p= 0.005)), however, this was not the case for diagnostic nasal endoscopies (n=11).[61] For nasal endoscopies (with debridement), particle size distribution of samples were comparable with pre-procedural measurements, but this outcome was not reported in relation to diagnostic nasal endoscopy.[61] In contrast to Shrimpton et al's (2022) and Chan et al's (2020) study where a decrease in particle counts was seen with suctioning,[81, 108] a significant mean increase was seen during suction use (2,973 p/ft^3 (CI 1,419-4,529, p=0.001)).[61]

Manual face mask ventilation

Two studies were included that reported on manual face mask ventilation.[81, 82] In Shrimpton et al's 2022 study, particle concentrations for manual face mask ventilation were compared to tidal breathing and coughing for 18 subjects.[82] Median particle concentrations during face mask ventilation, both with (11 particles/L) and without (3 particles/L) an artificially created leak were much lower than that recorded during tidal breathing (191 particles/L, p=0.002 and p=0.001 respectively).[82] Peak particle concentrations during face mask ventilation, both with (120 particles/L) and without (60 particles/L) a leak were lower than the peak particle count detected during a cough (1260 particles/L, p=0.001 and p=0.002 respectively).[82] However, as with other similar studies there was no assessment of particle size. In another study by Shrimpton et al, median particle concentrations during manual facemask ventilation of sedated patients were not significantly different from background levels (p= >0.99).[81] Authors do not report on particle size distribution, therefore, it is not possible to ascertain how particle count changes are distributed across the range of particle sizes between 0.3-10µm.[81] This limited evidence base suggests that manual facemask ventilation is associated with lower peak particle counts than forced coughing.

Tracheal intubation/extubation

One study assessed tracheal intubation/extubation. In Shrimpton et al's study, median particle concentrations during tracheal intubation were not significantly different to background levels (p=>0.99) and extubation particle concentrations were not significantly different to awake tidal breathing (p=0.1).[81] There was no assessment of particle size, therefore it is not possible to ascertain how particle count changes are distributed across the range of particle sizes between 0.3-10µm.[81]

Lung function tests

Two studies were included that assessed lung function tests.[71, 84] One study found that for healthy volunteers (n=33) and patients with reduced lung function but no viral infection (n=10), standard spirometry (with a filter) and peak flow measurements (with a filter) were not associated with higher peak particle counts (0.5-20µm) compared to forced coughing.[84] Compared to a filtered peak flow, voluntary cough mean peak particle counts were 18 times higher in healthy volunteers and 145 times higher in patients (both p=<0.01).[84] Compared to spirometry (with a filter) voluntary cough mean peak particle counts were 56 times higher in volunteers and 22 times higher in patients with lung disease (both p= <0.01).[84] Significant particle production, above background levels, was not detected for the Fractional Exhaled Nitric Oxide (FeNO) device. This study had a small sample size with lack of power calculation and lack of reporting on particle size distributions and how this may differ between lung function tests and/or respiratory events.[84] Subat et al assessed particle generation during respiratory peak flow testing of five healthy volunteers.[71] Mean concentration of particles, between 0.02 and 1µm, during peak flow testing, were significantly higher than tidal breathing, (p=0.01), however, this conclusion is limited to this small particle size range sample.[71] Particle generation also varied between the five peak flow meters used and it is unclear which value was used for comparative analysis.[71] Based on this limited evidence base it is clear further research is needed regarding lung function tests and particle production.

Dental procedures

One study assessed particle production during dental ultrasonic scaling.[117] Graziani et al's study involved air sampling before and after eight adult patients underwent ultrasonic scaling of their anterior teeth. The dental surgeries used for this study had no natural or mechanical ventilation.[117] There was a significant particle count increase (sized 0.5μm and 1μm) at the end of instrumentation and 15 mins afterwards compared to the beginning of instrumentation (p=<0.05), but no significant change for particles in the size range 0.3 μm.[117] Particle counts appeared to return to baseline levels at differing times post procedure according to particle size. Particles 0.5μm in size had returned to baseline levels at 60 minutes post instrumentation, 1μm at 45 minutes, 3μm at 15 minutes. Particles of size 5μm and 10μm dropped below baseline levels during or just after instrumentation up until 105 minutes afterwards.[117] Particles of 0.3μm in size appeared to not have returned to baseline levels by 105 minutes post-instrumentation.[117] This study's findings should be interpreted with caution due to the small sample size. It is also unclear from the paper how much time elapsed between each sampling session and whether this would represent sufficient time for particle fallout and/or clearance.

In another dental study hand scaling, routine extractions and 3in1 use (water only) did not appear to significantly contaminate the air, above background levels, with particles (0.5-20μm in size).[85] Procedures such as drilling (high speed/slow speed/surgical), 3in1 with air use and ultrasonic scaling appeared to be higher than baseline peak forced patient cough measurements, however the source of these particles is unknown (for instance instrumental irrigant or respiratory tract fluid).[85] As an additional exploratory exercise, dental procedures were performed on both a manikin head and human subjects with comparison of particle size distributions. Authors assessed the distributions in an attempt to distinguish between procedures which produced aerosols with salivary contamination and those that might be purely instrument derived.[85] The study supported the concept that particles (sizes 0.5-20μm) produced during ultrasonic scaling, 3-in-1 syringe use (air + water) and surgical drilling, may be largely or wholly instrument, rather than patient, derived whereas high and slow speed drilling appeared to have different size distributions compared to the phantom head measurements, potentially suggesting a

non-instrumental source of particles.[85] However, these conclusions are based on weak evidence and this study cannot be used in isolation to confirm this hypothesis.

Continuous Positive Airway Pressure and Non-invasive Positive Pressure Ventilation

Four studies assessed either continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation (NIPPV).[62, 86, 89, 93] Simonds et al.'s 2010 observational study involved healthy subjects (n=12), patients with coryzal symptoms (n=11) and chronic lung disease patients with acute respiratory infection exacerbations (n=21).[86] Particle production during various procedures was compared to baseline particle counts, which involved subjects breathing and coughing. At 1m, NIPPV using a vented mask was associated with a significant increase in particles in the following size ranges 3-5µm (p=0.047) and 5-10µm (p=0.018) for coryzal patients but not healthy or chronic lung disease patients.[86] NIPPV (20/5cm H_2O) using a vented mask was associated with a significant increase in large particles (>10µm) at source, both in chronic lung disease (CLD) patients (p=0.042) and in subjects with coryzal symptoms (p=0.044) but not in healthy individuals (p=0.379).[86] In contrast to NIV using a vented mask, no significant increase in any particle size ranges (0.3-10µm) at source or at a 1m distance was seen with use of the non-vented NIPPV circuit with exhalation filter (20/5cm H_2O) which suggests that it may be a useful particle dissemination mitigation measure.[86] This study's main limitations include small sample sizes, variability of NIPPV settings for patients as these were based on clinical need and not standardised in line with settings for healthy or coryzal symptom participants (20/5cm H_2O), absence on reporting of activity during baseline sampling period where participants were asked to do "a series of spontaneous coughs" whilst wearing and not wearing a surgical mask as well as unknown room parameters such as temperature, humidity, air flows and background particle counts.[86] Particle production during CPAP delivery was assessed in another study.[89] CPAP (with exhalation port filter and non-humidified, 15cm H_2O pressure) was associated with significantly less particle production when breathing, speaking and coughing (p=<0.0001 for all comparisons). "Even with a large, induced face mask air leak (>50 L/min), the aerosol emission measured over that leak during coughing was

lower than in [coughing] participants not receiving CPAP (0.12 vs 1.52 particles/cm^3, p= <0.0001)".[89] A third study assessed particle production during non-invasive ventilation (NIPPV 12/5 cm H_2O and 20/10 cm H_2O).[62] In 10 healthy participants; neither the median particle number nor size of particles significantly changed with either ventilation modality. This was the case during normal breathing, talking, deep breathing, and forced coughing (all p=<0.05).[62] In Wilson et al's 2021 study, significant total particle count increases were observed for single and dual circuit NIPPV at 15/10, 20/10 and 25/10cm.H_2O (all p= <0.001) and dual circuit NIPPV at 5/5, 10/10, 15/10, 20/10 and 25/10cm.H_2O (p= 0.031 and p= <0.001 respectively), compared to the tidal breathing baseline measurements.[93] NIPPV was associated with an increase in average total particle counts compared to tidal breathing (1.9 to 7.8-fold increases). Non-procedure associated respiratory activities for example talking, shouting, coughing, exercise or FEV manoeuvres, were associated with even larger total particle count fold increases of 34.6 to 370.8.[93] During exercise, use of NIPPV-S 20/10 and NIPPV-D 20/10 were associated with particle count reductions of 30 to 60%, though only significantly during NIPPV-S (p=0.002).[93] Based on this limited evidence base, NIPPV or CPAP with use of an exhalation filter, appears to produce more particles than breathing but less than forced coughing.

Chest physiotherapy

Only one study associated with chest physiotherapy was identified.[86] Simonds et al.'s 2010 observational study involved chronic lung disease patients with acute respiratory infection exacerbations (n=21). Particle production (0.3->10µm in size) during chest physiotherapy was compared to baseline particle counts (breathing and coughing).[86] The chest physiotherapy procedure was described as follows; "cycles of deep breathing with percussion or shaking to loosen any secretions, followed by an assisted cough initiated manually, augmented by the physiotherapist performing inward and upwards pressure on the lower thorax to aid expectoration, after which the patient rested and cycles were repeated for 10 minutes".[86] Chest physiotherapy was found to create an increase in large particles (>10µm) next to the subjects' face (p=0.003), but no significant increase in any particle size at one metre.[86] This study's main limitations include a small sample size, limited reporting of activity during baseline sampling period where participants were asked to do "a series of

spontaneous coughs" whilst wearing and not wearing a surgical face mask, as well as unknown room parameters such as temperature, humidity, air flows and background particle counts.[86] Based on this one small study, the chest physiotherapy administered to this cohort did not appear to generate significantly more particles of 0.3->10µm in size at a one metre distance or particles of ≤10µm in size at source, when compared to a series of coughs.

Oxygen therapy

Two studies were identified which assessed oxygen therapy and particle production.[62, 86] Simonds et al.'s 2010 observational study involved healthy subjects (n=12), patients with coryzal symptoms (n=11) and chronic lung disease patients with acute respiratory infection exacerbations (n=21).[86] Particle production during various procedures was compared to baseline particle counts (breathing and coughing). Oxygen therapy, via a 60% Ventimask (15L/min), for healthy and coryzal symptom participant group, and 24% Venturi mask (2L/min) for chronic lung disease patients, did not increase particle count in any size range (0.3-10µm) for any subject group.[86] This study's main limitations include small sample sizes, limited reporting of activity during the baseline sampling period where participants were asked to do "a series of spontaneous coughs" whilst wearing and not wearing a surgical face mask, as well as unknown room parameters such as temperature, humidity, air flows and background particle counts.[86] Gaeckle et al's study involved 10 healthy participants and assessments of particle production during varying respiratory activities and oxygen delivery (non-humidified nasal cannula at 4L/min and non-humidified face mask at 15L/min).[62] Neither the median particle number nor size of particles significantly changed with either oxygen modality tested. This was the case during normal breathing, talking, deep breathing, and forced coughing (all p=<0.05).[62] Limited evidence suggests that breathing with oxygen delivery of up to 15L/min via a face mask does not produce more particles than forced coughing.

Nebulised saline administration

In Simonds 2010 study, nebulised saline increased mean particle counts in the following size range categories for all subject groups: 0.3-0.5, 0.5-1, 1-3 and 3-5µm at the subject's face and 1m away.[86] Nebulised saline increased particle counts in

the following size range categories for healthy subjects: 5-10, >10µm at subject's face but not one metre away. Nebulised saline did not increase particle counts of 5-10 or >10µm at 1m away for any subject group.[86] Particles contaminated with respiratory secretions, or of respiratory tract origin, cannot be distinguished from those produced by the nebuliser itself. This study's main limitations include small sample sizes, limited reporting of activity during baseline sampling period where participants were asked to do "a series of spontaneous coughs" whilst wearing and not wearing a surgical face mask, as well as unknown room parameters such as temperature, humidity, air flows and background particle counts.[86] More research is required on nebulised saline, including analysis of the origin of particles.

High flow nasal oxygen

Three studies assessed high flow nasal oxygen (HFNO) delivery.[62, 89, 93] Compared to tidal breathing, particle counts increased during HFNO administered at 20, 40 and 60 L/min, however, only HFNO at 60L/min was associated with a significant increase (2.3-fold, p=0.031).[93] HFNO appeared to increase particle production for quiet breathing but not to the same degree as non-procedural respiratory activities for example talking, shouting, coughing, exercise or forced expiratory volume (FEV) manoeuvres, which were associated with fold increases of 34.6-370.8.[93] In contrast to particle count changes seen during breathing with HFNO, particle counts reduced when HFNO was used at 60L/min, during talking and forced expirations with a significant reduction seen during coughing, where emissions were halved (p = 0.028).[93] In Gaeckle et al's study involving 10 healthy participants, neither the median particle number nor size of particles significantly changed with any high flow nasal oxygen modality tested (10L/min, 30L/min and 50L/min).[62] This was the case during normal breathing, talking, deep breathing, and forced coughing (all p=<0.05).[62] In Hamilton's 2022 study, HFNO was associated with increased particle number concentrations when compared to breathing (1.86 particles/cm^3 for HFNO 60L/min (n=20) compared to 0.03 particles/cm^3 when breathing (n=24) p= <0.0001).[89] However, authors hypothesise that a significant proportion of the generated particles were from the equipment itself as; "aerosol was emitted [from the HFNO equipment] even when the machine was unattached to the patient" and the addition of a filter, between the device and patient, reduced particle production to

0.006cm^{-3} when breathing compared to 2.4cm^{-3} with no filter.[89] This hypothesis was, however, based on one subject and further research is required to determine whether particles produced during HFNO measurements are contaminated with respiratory fluids or not.[89] Based on the limited evidence presented, HFNO at flow rates of 20 and 40L/min do not appear to produce significantly more particles than tidal breathing. HFNO at 60L/min appears to be associated with increased particle production when compared to tidal breathing but is likely less than coughing particle production and may even have a mitigating effect causing decreased particle production during coughing, however, further research is needed to explore this phenomenon.

Supraglottic airway insertion/removal

In a 2021 UK based study, particle concentrations were measured during supraglottic airway (SGA) insertion and removal for 12 patients.[87] Concentrations were compared to background levels and baseline measurements (which involved 30 seconds of tidal breathing by the patient). There was some inter-participant variation with three having face mask ventilation administered immediately before insertion and eight having a period of manual ventilation to confirm airway patency after insertion.[87] One participant required two SGA insertion attempts. The median concentration of particles recorded during the 11 SGA first pass insertions was 1.3 particles/l (IQR 1.0–4.2 [range 0–6.2]).[87] This was not significantly different to median background levels or baseline measurements (p= 0.31 and p= 0.27, respectively). SGA removal (n = 12) produced a median particle concentration of 2.1 particles/l (IQR 0–17.5 [range 0–26.2]).[87] This was not significantly different to median baseline measurements (p= 0.84). The study does not provide a comparison of the size distribution profiles of SGA insertions or removals compared to baseline tidal breathing samples.[87] As previously outlined, one participant required two SGA insertion attempts. The re-insertion sequence was associated with increased particle generation: a total of 114 particles were detected compared to 4 during uneventful insertions.[87] Further research is needed to explore this phenomenon. Overall, Shrimpton et al's 2021 study provides evidence that uneventful SGA insertion or removal does not create a significant increase in median airborne particle

concentration above tidal breathing levels, however, differences between procedural and baseline measurement particle size distributions are not reported.[87]

Myringotomy and tympanostomy tube insertion

Campiti et al assessed particle generation during myringotomy (an incision into the ear's tympanic membrane to relieve pressure and/or drain fluid/pus) and tympanostomy tube (MT) insertion (to maintain incision patency) for five to nine paediatric patients (reported as nine ears).[69] There was no difference between baseline and procedural concentrations for particles 0.90 to <2.69µm (p=0.94) or 2.69-10µm (p=0.11) in size. Baseline samples involved measurements conducted over 60 seconds post induction of anaesthesia but pre-procedure.[69]

Tonsillectomy with monopolar electrocautery

Based on four procedures, tonsillectomy with monopolar electrocautery was associated with a statistically significant increase in aerosol concentrations compared to baseline when considering all sizes measured (0.3-10µm).[69] Baseline samples involved measurements conducted over 60 seconds post induction of anaesthesia but pre-procedure.[69]

3.5.7 Pathogens in the air – post source departure

One study provided data associated with viable pathogen detection in the air space previously occupied by an infected individual[83] and three experimental studies assessed the viability of pathogens, within air suspended particles, over time.[95-97] Based on the limited evidence base it can be concluded that viable RSV virus may be detectable within the air two hours post infectious source departure[83] and that exhaled *S. aureus*, *P. aeruginosa* and certain strains of gram-negative bacteria (*S. maltophilia, Burkholderia spp. and Achromobacter spp*.) can remain viable in air-suspended particles for 45 minutes.[95, 97] However, whether these particles would remain airborne for this length of time in vivo is unclear. It is also unknown as to whether viral loads within the air would remain high enough over prolonged periods to cause infection.

UKHSA state, without supportive citations, in their 2021 ventilation guidance, that "while larger droplets fall quickly to the ground, aerosols containing the virus can remain suspended in the air for some time, including after an infected person has left the area".[123]

Kulkarni et al's 2016 study demonstrated that two hours following discharge of three RSV infected patients from cubicles with six air changes per hour, viable RSV virus, although reduced from previous readings, was still detectable in the air.[83] Mean total plaque forming units (PFU) per 849L air sample was 27,850 PFU (+/- 25,452) before discharge but was reduced to 6,175 PFU (+/- 7,442) 2 hours post discharge.[83] It is unclear what procedures these patients underwent during sampling. The mean room temperature was reported to be 22.9°C (+/-1.5) and mean relative humidity was 36.7% (+/-5.7).[83] (Kulkarni 2016) Limitations of this study include specificity to infants with unknown medical interventions, a lack of staff or parent testing and a particular environment associated with a specific air change rate, temperature and humidity.[83]

In Wood et al's 2019 cystic fibrosis patient study, certain strains of gram-negative and *S. aureus* bacteria remained viable within particles in the air for 45 minutes.[95] Cough aerosols of 15 CF patients with GNB positive sputum samples (18 associated GNB species) and 16 patients with *S. aureus* positive sputum samples (16 associated *S. aureus* species) were sampled.[95] To assess the viability of cough aerosol bacteria over time, three separate extractions of aerosol samples from a rotating drum chamber were taken at 5, 15 and 45 minutes, following a two-minute coughing period by patients into the connecting mouthpiece.[95] For the GNB patient group, temporal samples were obtained for 14 patients (17 associated GNB species), nine of which were culturable at 45 minutes post-production. For the *S. aureus* patient group four of 16 species were culturable at 45 minutes.[95]

Two studies assessed the viability of *P. aeruginosa* in cough aerosols over time.[96, 97] In Stockwell et al's study, following a two-minute coughing period by patients, three separate extractions of aerosol samples from the rotating drum chamber, were conducted at 5, 15 and 45 minutes. No viable *P. aeruginosa* was obtained from five- or 45- min post-production samples, but two out of seven participants had positive cultures at 15 minutes, with an average of 1 CFU.[96] In Knibbs et al's 2014 study *P. aeruginosa* aerosol samples from 14 of 18 participants remained viable for a duration

of 45 minutes. A significant decrease in CFU counts was seen with increasing duration (p=0.046).[97] Positive aerosol samples were associated with both small (<3.3μm) and large (>3.3μm) particle size fractionated samples.[97] These studies suggest that *P. aeruginosa* bacteria can remain viable within small particles (<3.3μm) in the air for 15 to 45 minutes when artificially kept aloft.

3.5.8 Other correlations

Seventeen studies looked for correlations between the characteristics of pathogens and/or particles released into the air and participant demographics, clinical sample findings or specific features of infection.[60, 66, 74, 75, 77, 78, 84, 91, 92, 94, 95, 98, 106, 110, 115, 116, 121] The limited evidence base indicates that there may be a correlation between sputum and cough *P. aeruginosa* CFU counts in cystic fibrosis (CF) patient cohorts,[91, 92] that there may be no significant correlation between influenza RNA viral load in nasopharyngeal swab and aerosol samples[74, 77] and that the likelihood of detecting SARS-CoV-2 RNA in exhaled breath may decrease as days from symptom onset increase.[115, 121]

Aerosol viral/bacterial load and clinical samples

Six studies looked for a correlation between viral or bacterial loads/counts within clinical samples (sputum or nasopharyngeal swabs) and exhalation samples, reporting contrasting results.[74, 77, 91, 92, 95, 116] Both Wood et al's 2018 study and Wainwright et al's 2009 study, identified a statistically significant association between sputum and cough *P. aeruginosa* CFU counts in CF patient cohorts; (n=19, r=0.55, p=0.01) and (n=20, r=0.58, p=0.008) respectively.[91, 92] A further study by Wood et al included 16 CF patients with a history of *S. aureus* respiratory infection and 15 with a history of GNB respiratory infection.[95] A correlation was identified between bacterial sputum and aerosol concentrations at two metres for both GNB species (r=0.50, p=0.035) and *S. aureus* (r=0.66, p=0.005).[95] In a 2022 COVID-19 study involving a small, young cohort of infected participants with RNA positive exhalation samples (n=10), there was no significant association identified between the viral loads of nasopharyngeal (NP) swabs and aerosol samples.[116] Two studies presented data on NP swabs and exhalation air samples from a young cohort of influenza infected participants.[74, 77] In Yan et al's 2018 study involving 142 influenza infected volunteers

between the ages of 19 and 21 years old, viable influenza virus was detected in 52 fine aerosol (0.05-5μm) samples following 30 minutes of breathing and speaking (cone sample collection), however, it is unclear as to how many subjects these positive samples are associated.[74] Milton et al's 2013 study involved a young cohort of 37 influenza infected participants (median age=19) with samples collected at close range (cone sample collection) during 30 minutes of breathing and coughing (30 x coughs).[77] Both studies found no significant correlation between viral RNA load in the nasopharyngeal swab sample and that of the coarse (p=0.16 and p=0.31 respectively) or fine fraction aerosol samples (p=0.48 and p=0.08 respectively).[74, 77]

Aerosol pathogen positivity rates

In seven studies, pathogen detection rates in aerosols were examined alongside a multitude of factors including the respiratory activity performed (for example coughing, breathing), symptoms, days since symptom onset, sex, virus variant, treatment history, smoking history, asthma status, nasopharyngeal swab cycle threshold (Ct) values or a need for oxygen therapy.[60, 66, 74, 94, 106, 115, 121] The main limitation of these studies is likely specificity, with unique pathogens, including specific circulating strains, and participant cohorts.

An observational study involving 53 influenza A infected, but otherwise healthy, college students, demonstrated that viable influenza A was disseminated into the air via forced coughing (positive aerosol samples for 28 of 53 sampled persons) and forced deep exhalations (positive aerosol samples for 22 of 52 of sampled persons).[60] There was no difference in rates of positive air samples for these two differing respiratory activities (p= 0.2207), however, in addition to other limitations, the process of forced coughs and exhalations may also not mirror natural processes therefore limiting applicability.[60] Gralton et al. and Alsved et al. also examined the effect of respiratory activity on aerosol pathogen positivity rates, but in relation to COVID-19 RNA detection and parainfluenza and rhinovirus RNA detection respectively.[94, 115] Gralton et al's Australian 2013 study showed that viral parainfluenza and rhinovirus RNA can be detected from infected persons' breathing or cough exhalations.[94] There was no significant difference regarding frequency of viral RNA detection between breath (10 minutes) and cough samples (10 x coughs) (p= 0.712)[94] whereas Alsved et al found that there was a higher fraction of

SARS-CoV-2 RNA positive aerosol samples from either singing 42% (16/38) or talking, 30% (11/37) compared to breathing, 8% (3/38) (p=0.001 and p=0.019 respectively).[115]

Three studies looked for potential correlations between the rates of RNA positivity in exhalations of COVID-19 infected participants and reported symptoms.[106, 115, 121] Alsved et al. outlined that cases reporting a cough were more likely to have positive aerosol samples (OR 13, 1.4–120, p=0.02)[115] and similarly in Sawano's 2021 study, investigators identified that significantly higher detection rates of viral RNA were associated with presence of a cough or fever (p=<0.01 and p=0.01 respectively).[121] In contrast to these findings, however, Coleman et al reported that clinical symptoms were not significantly different between COVID-19 infected participants with and without detectable SARS-CoV-2 RNA in respiratory exhalations.[106] In Yan et al.'s 2018 study the presence of viable influenza in aerosols did not appear to correlate with participants' temperatures measured at time of sampling or reported symptoms.[74]

Two studies assessed potential correlations between the rates of RNA positivity in exhalations of COVID-19 infected participants and days from symptom onset.[115, 121] Alsved et al. reported, based on 38 participants, that as days from symptom onset increased, likelihood of detecting SARS-CoV-2 RNA in exhaled breath decreased (OR 0.55, 0.30–1.0, p=0.049).[115] This finding was reflected in Sawano et al's 2021 study where investigators reported that significantly higher detection rates of viral RNA were associated with being less than three days from symptom onset (p=<0.01).[121]

In Sawano's 2021 study, investigators found, based on 48 participants, that significantly higher detection rates of SARS-CoV-2 viral RNA in exhaled breath samples, were associated with a need for oxygen administration (p=<0.01) or mechanical ventilation (p= 0.04).[121] In another COVID-19 infection study involving 38 participants, authors found that RNA aerosol-positive cases were more likely to have lower nasopharyngeal (NP) swab Ct-values (i.e. a higher NP viral load) than aerosol-negative cases (p=0.02).[115]

Coleman et al reported in their 2022 COVID-19 study that sex and virus variant type were not significantly different between participants with and without detectable SARS-CoV-2 RNA in respiratory exhalations.[106] In 2004, Fennelly et al. identified culturable Mtb within the cough exhalations of four of 16 TB infected patients.[66] Production of culturable aerosol following five minutes of coughing was associated with lack of treatment in the preceding week(s) (p= 0.007) but not sex, or presence of lung cavitation, however, study sample size was likely too small to detect some significant correlations if present.[66] Yan's 2018 observational study presented data on nasopharyngeal swabs and exhalation air samples from 142 influenza infected volunteers between the ages of 19 and 21.[74] In this study, viable influenza virus and RNA was detected in fine aerosol (0.05-5μm) exhalations of individuals following 30 minutes of breathing and speaking. Aerosol viral RNA shedding did not appear to correlate with asthma history, smoking, or influenza type.[74]

Bacterial or viral load of aerosols

Four papers presented data on factors which may correlate with quantity of bacteria or virus in exhaled aerosols.[74, 91, 110, 121] Yan et al's 2018 influenza study examined days from symptom onset and aerosol sample viral load.[74] Yan et al presented data on NP swabs and exhalation air samples from 142 influenza infected volunteers between the ages of 19 and 21. In this study, viable influenza virus and influenza RNA was detected in fine aerosol (0.05-5μm) exhalations of individuals following 30 minutes of breathing and speaking.[74] Compared with one day post symptom onset, authors found that quantity of viral RNA shed into fine aerosols on day three was significantly less (effect estimate 0.24 [0.09–0.59] p=<0.01).[74] Yan et al also found that number of viral influenza RNA copies in fine aerosol samples was moderately correlated with cough frequency during sampling (r =0.45, p= <0.0001).[74] In Wainwright et al's 2009 study, no significant correlations between *P. aeruginosa* CFU counts in cough exhalations and patient factors such as age, gender, current exacerbation status, forced vital capacity, maximal inspiratory or expiratory pressure, percentage predicted FEV1, strength of cough or number of coughs, were identified.[91] In Sawano's 2021 study, investigators identified a significant association between SARS-CoV-2 RNA viral load in the exhaled breath condensate of their cohort of hospitalised COVID-19 infected patients and their need for mechanical

ventilation (p= <0.05).[121] Findings from Jones-Lopez et al's 2013 study suggested that there was significantly greater odds of infection with TB if housed with a high-aerosol producing TB index case (defined as producing >10 CFUs following five minutes of coughing) compared to a low producer (OR 4.81 [1.20–19.23] p=0.03).[110] However, authors report that some index cases had received treatment (≤5 days' worth), this, as well as immune status of contacts, is not accounted for in the comparison of household contact infection rates.[110]

Particle production and age

Two studies explored the relationship between respiratory emissions and age.[98, 106] Particle emission rates during breathing, speaking and singing were compared between 15 adults and 15 children in Fleischer et al's 2011 study.[98] Emission rates for all respiratory activities were significantly lower for children but particle size distribution profiles remained similar. On the linear scale, the particle emission rate for all respiratory activities, for the child group, was reduced by a factor of 4.3 when compared with the adult group (p=< 0.001).[98] Coleman et al reported in their 2022 COVID-19 study that age was not significantly different between participants with and without detectable SARS-CoV-2 RNA in respiratory exhalations.[106]

S. aureus dissemination from colonised individuals

Bischoff's 2006 study, although specific to a small group of young persons (n=11), suggested that the mean number of *S. aureus* (CFU), in the nose or pharynx, does not change significantly after rhinovirus exposure (IRR, 1.02; P=0.888) but that sneezing significantly increases the amount of *S. aureus* bacteria disseminated into the air from the respiratory tract from nasally colonized individuals.[75] A comparison between sneezing and non-sneezing sessions showed a 4.71-fold increase [3.27-6.78] in *S. aureus* dispersion associated with sneezing and a 17.45-fold increase [7.48–40.71] for those with allergies (both p= <0.001), however, it is unclear how many participants were classed as having allergies.[75]

Particle counts and co-morbidities

Shiekh et al found in their UK 2022 study, that patients with lung disease (n=10) appeared to generate higher particle counts than healthy volunteers (n=33) when

breathing (0.29 vs 0.04 particles/cm^3, p<0.01) and speaking (0.20 vs 0.10 particles/cm^3, p=0.04), but not when coughing (1.45 vs 1.61 particles/cm^3, p>0.2)".[84]

Particle production and respiratory infection

Lindsley et al's 2012 study suggested that total volume of aerosols in picolitres, within a forced cough, may increase during influenza infection (26.4pL/cough to 38.3pL/cough (p = 0.0143)), however, median diameter of cough particles and air volume of coughs did not significantly change.[78] Due to the limitations of this study further conclusions cannot be drawn and more research is needed with greater sample sizes to assess the effects of respiratory infection on particle production.

3.6 Can person-to-person transmission of infection be described/defined beyond the current categories of contact/droplet and/or airborne?

Of the six organisational expert opinion pieces (all graded SIGN level 4) included for this research question, one was published by the World Health Organization,[2] three were from the U.S.A[3, 124, 125] and two were from Canada.[12, 126] All were related to healthcare IPC, with one having a focus on epidemic and pandemic acute respiratory infections.[2]

Some IPC guidance sources present transmission modes which serve as an addition or alternative to the traditional categories of contact, droplet and airborne.

In their 2016 guidance, the CDC refer to four modes of transmission: contact, splash and spray, inhalation, and sharps injuries.[125] In this context the term 'inhalation' appears to have been used as a proxy for the traditional airborne concept as authors describe it as involving "germs […] aerosolized in tiny particles that survive on air currents over great distances and time".[125] Authors provide a separate description of "close range inhalation" which they state "occurs when a droplet containing germs is small enough to breathe in but not durable over distance".[125] Similarly, a 2022 American Society of Heating Refrigerating and Air-conditioning Engineers (ASHRAE) position document proposes use of the following terms "(1) inhalation of aerosols, (2) spray of large droplets, and (3) touching a contaminated surface".[124] Authors state

that the first term of 'inhalation of aerosols' "supplants the traditional airborne route, which was assumed to apply only at long distance, while the second and third correspond to the traditional droplet and fomite (or contact) routes".[124] Authors thereby promote the concept of 'inhalational transmission' occurring at any distance.[124]

Regarding particles which are "transferred through the air", three categories of transmission are presented in a Canadian guidance figure.[12] The term droplet is linked to transmission occurring when face-to-face and up to, or less than, 2m away, with involvement of particles sized 50-100μm.[12] The term airborne accompanies a description of transmission occurring when face-to-face and up to a distance of "beyond the room" away, with involvement of particles sized <10μm.[12] A transmission route is presented between these two descriptions and therefore, by design, not aligning perfectly with the airborne or droplet terms.[12] This transmission route involves particles of sizes 10-50μm and occurs "from face-to-face to within the room".[12] This transmission mode is not given a specific descriptive term. This figure appears to present the continuum of particles and distances associated with exposure to a pathogen transmitted via the air, however, it is not a fully formed concept and practical applicability of the framework is unclear.[12]

Some guidance outlines that pathogens are not exclusively transmitted via one route and that routes of transmission have differing likelihoods attributed to them based on pathogen and encounter circumstances. Terms such as "predominant mode", "more frequent route" and "rare occurrence" are used.[2, 3] Similarly, the Canadian Government Pathogen Risk Assessment includes terms which indicate likelihood of transmission via a specific route - "none; low, unlikely; moderate, possible; high, preferred route; unknown".[126]

The CDC[3] and WHO[2] make reference to an opinion piece by Roy and Milton (2004) who proposed the following airborne transmission descriptions: 1) "obligate: under natural conditions, disease occurs following transmission of the agent only through inhalation of small particle aerosols (e.g., tuberculosis)" 2) "preferential: natural infection results from transmission through multiple routes, but small particle aerosols are the predominant route (e.g., measles, varicella)" and 3) "opportunistic: agents that naturally cause disease through other routes, but under special

circumstances may be transmitted via fine particle aerosols".[127] These descriptions are still encapsulated within the restrictive, conventional 'airborne' definition and do not represent a new way of describing air mediated transmission but rather a risk classification for airborne transmission.

3.7 What are transmission-based precautions (TBPs)?

Nineteen guidance documents (all graded SIGN level 4 - expert opinion) contributed to answering this research question. Three were published by the World Health Organization,[1, 2, 128] two were from Australia,[6, 7] with one from each of the following countries: Northern Ireland,[13] England,[9] Canada,[12] New Zealand,[47] Hong Kong[11] and Ireland.[35] Eight guidance documents were sourced from the U.S.A.[3-5, 129-133] Most were general IPC guidelines with some having a focus on particular health and care settings, such as primary care[35, 128] or care homes.[4, 130, 132, 133] Some applied to particular groups of pathogens for example; multidrug resistant organisms (MDROs)[131, 132] or acute respiratory tract infections.[2, 9]

According to guidance at time of writing, transmission-based precautions (or additional precautions)[7, 12] are a set of infection control steps referred to as the second tier of basic infection control[11, 129] with their implementation being outlined as an addition to standard or routine infection control practices.[1, 3, 7, 11-13, 47, 128, 129] Standard infection control precautions (SICPs) are IPC measures used to prevent transmission of healthcare associated infection.[134] SICPs should be applied to all patients, under all health and care circumstances,[134] whereas use of additional transmission-based precautions is widely cited to be required following suspicion, or diagnosis of, an infection or colonisation with an infectious agent.[1, 11, 12, 47]

Current guidance presents transmission-based precautions as three categories or groups; contact precautions, droplet precautions and airborne precautions, each of which corresponds to three historically hypothesised main modes of person-to-person infection transmission; contact transmission, droplet transmission or airborne transmission.[1-3, 6, 7, 11-13, 35, 47, 128] Guidance outlines that grouped contact, droplet or

airborne precautions can be used individually or in combination, depending on the perceived transmission mode(s) of the pathogen.[3, 9, 12]

CDC authors emphasised that "transmission-based precautions category assignments reflect the predominant mode(s) of transmission" and were "assigned if there was strong evidence for person-to-person transmission via droplet, contact, or airborne routes in healthcare or non-healthcare settings and/or if patient factors […] increased the risk of transmission".[3] Standard precautions were recommended for pathogens with "a low risk for person-to-person transmission and no evidence of healthcare associated transmission".[3] Evidence based assignation of pathogens to predominant transmission routes is also clear in older CDC guidance where a hierarchy of 'evidence for airborne transmission' presented:

- "Numerous reports in health-care facilities"
- "Occasional reports in health-care facilities (atypical)"
- "No reports in health-care facilities/known to be airborne outside"
- "Under investigation".[36]

Contact precautions

Contact precautions are widely cited to include the following: single room isolation[2-7, 12, 13, 129, 131, 132] or cohorting with other patients/residents infected/colonised with the same pathogen,[2-4, 12, 13, 132] healthcare worker (HCW) gloving (either on entry to the patient room/area or in anticipation of patient contact),[2-5, 7, 9, 12, 129, 132] HCW gowning (either on entry to the patient room/area or in anticipation of patient contact),[2-5, 7, 12, 129, 132] restriction of patient movement,[2-4, 6, 13, 129, 132] dedicated patient care equipment,[2-5, 7, 9, 12, 129, 132] enhanced cleaning regimes with a focus on frequently touched surfaces[3, 5, 9, 12, 129] and specific patient transfer protocols including appropriate covering of potentially infectious lesions[3, 5, 12] and informing receiving departments of patients contact precaution status.[3, 5, 13]

Less frequently recommended contact precautions include: a dedicated patient toilet and sink,[12] a dedicated staff sink,[12] room signage indicating contact precaution patient status,[13] minimising numbers of visitors,[12] performance of hand hygiene by

patients before leaving their room,[12] adequate spatial separation from others[3, 5] and use of privacy curtains.[3, 12]

Droplet precautions

Droplet precautions are widely cited to include the following: single room isolation[2, 3, 5, 7, 9, 12, 13, 129] or cohorting for patients infected with the same pathogen,[2, 3, 9, 12, 13] medical/ surgical mask use by healthcare workers,[2, 3, 5-7, 9, 13, 129] restriction of patient movement,[2, 3, 6, 9, 12, 13, 129] patient mask wearing when out with room,[2, 3, 5, 9, 12, 13, 35] promotion of patient respiratory hygiene/cough etiquette,[3, 5, 9, 129] spatial separation from others,[2, 3, 5, 9, 12, 35] privacy curtains between beds[3, 9, 12] and specific patient transfer protocols including informing receiving staff of patient's droplet precaution status.[3, 5, 13] Droplet precaution guidance also emphasises that 'no special air handling or ventilation' for the patient room are required[5, 9, 13] and that if the patient is masked, there is no need for HCW masking during patient transfer.[3, 5, 9, 12]

Less frequently recommended droplet precautions include: HCW eye protection,[129] room signage indicating droplet precaution patient status,[9, 13] dedicated patient care equipment,[3] airborne precautions for aerosol generating procedures (AGPs),[5, 9] dedicated waiting areas,[12, 35] restriction of susceptible HCWs entering patient room for specific pathogens,[12] patient performance of hand hygiene before leaving their room,[12] minimising number of visitors,[12] masking of visitors,[12] and a specification that doors of patient rooms can remain open.[12]

Airborne precautions

Airborne precautions are widely cited to include the following: use of a negative pressure isolation room[2, 3, 5-7, 12, 13, 129] with appropriate air change rates/ventilation,[2, 3, 12] respirator wearing by HCWs,[2, 3, 5-7, 13, 129] patient mask wearing when out with room,[2, 3, 5, 12, 13, 35] keeping the patient room door closed,[3, 12, 13] restricting patient movement,[2, 3, 6, 12, 13, 129] and use of specific patient transfer protocols including informing receiving staff of patient's airborne precaution status.[3, 5, 13] Airborne precaution guidance also emphasised that if patient is masked and infectious lesions were appropriately covered, there was no need for HCW masking during patient transfer.[3, 5, 129]

Less frequently recommended airborne precautions include: the air of the patient's room being exhausted to the outside or HEPA filtrated on re-circulation,[3, 12] daily visual monitoring of air pressure in patient room,[3] keeping windows of patient room closed,[13] promotion of patient respiratory hygiene/cough etiquette,[5, 129] post exposure immunisation for specific pathogens,[129] fallow times following patient leaving the room[3, 12] or following cough-inducing procedures,[5] mask wearing and isolation for any symptomatic persons attending with a patient for whom airborne precautions are deemed necessary,[3] impervious dressings for infectious lesions,[3, 5] dedicated patient care equipment,[3] dedicated waiting areas,[35] spatial separation from others,[35] end of day surgery scheduling with the minimum required number of personnel present,[5] applying filters to breathing systems/equipment,[5, 12] utilising air cleaning technologies if negative pressure isolation rooms are not available[5] and limiting and/or restricting visitation.[12]

Specific TBPs grouped together based on pathogen transmission routes (contact, droplet, airborne) should, in theory, provide a simpler approach to IPC precaution determination and implementation. However, close examination of IPC guidelines reveals that caveats or amendments to defined contact, droplet or airborne IPC precaution groupings are frequently outlined. Divergent TBP guidance was associated with specific pathogen types, patient factors, procedure types, care setting environments and local outbreak information - negating the function of a one-stop defined set of IPC precautions for large groups of pathogens. It is unclear whether precaution groupings should be used in a layered approach or be considered separate from one another. Often the same precautions are outlined across all three categories.

IPC guidance had recommendations specific to individual pathogens, embedded within their contact, droplet and airborne transmission-based precaution sections. In the airborne precautions section, the Northern Ireland IPC manual outlined use of an FFP3 respirator specifically for suspected or confirmed patient cases of multi- or extensively drug resistant tuberculosis (TB) but not for other pathogens which they describe as being transmitted via the airborne route.[13] The CDC recommend an N95 or higher-grade respirator for all forms of infectious TB but specified that a recommendation could not be made for the use of a respirator or surgical mask

when caring for patients with chickenpox, measles or disseminated herpes zoster, describing it as an “unresolved issue”.[3] Canadian guidance specifies that cohorting of TB patients was not appropriate due to potential differing strains.[12]

IPC guidance also gave unique recommendations based on patients’ presenting symptoms. Both the CDC and PHE advocated the use of single rooms for patients under droplet precautions but highlighted that patients with a cough should be prioritised.[3, 9] Similarly the CDC stated that single patient rooms were required for those being managed with contact precautions but should be prioritised for those “with conditions that may facilitate transmission” such as stool incontinence or uncontained draining wounds.[3] For droplet precautions, Canadian guidance recommends mask wearing by HCWs, but only for symptomatic patients.[12]

Canadian guidance provides TBP recommendations specific to certain care settings such as long-term care facilitates, where those being managed with droplet precautions are only restricted from group activities during their symptomatic period, or home care settings where deferral of routine care for those being managed with droplet precautions may be appropriate when respiratory symptoms are acute.[12]

Procedure-specific TBP recommendations were evident. Canadian guidance specifically recommends mask wearing for procedures that induce coughing[12] and the Association of periOperative Registered Nurses (AORN), in relation to airborne precautions, advises fallow times only following ‘cough inducing procedures’.[5]

Altered precaution recommendations were made based on specific patient factors. Canadian guidance suggests single rooms for those being managed with contact precautions with prioritisation considered for those with ‘cognitive impairment’.[12]

Local outbreak information was also associated with TBP guidance amendments. Canadian guidance outlines that in an outbreak situation or where there is continued transmission of *Clostridioides difficile*, rooms of infected patients should be cleaned with chlorine containing cleaning agents.[12]

In conclusion, TBPs are IPC steps which are grouped together based on a pathogen’s perceived transmission route(s), however, complexity is introduced when certain precautions, which would be implemented in line with this framework, are

deemed inappropriate based on the pathogen, patient symptoms, healthcare setting and/or local outbreak information.

3.8 When should TBPs be applied?

Twenty guidance documents (all graded SIGN50 level 4 - expert opinion), one Australian interrupted time series study[135] and one U.S.A retrospective cohort study[136] (both graded SIGN level 3) were included for this research question. In relation to the SIGN50 level 4 guidance, three were published by the World Health Organization,[1, 2, 128] two for England,[9, 10] two for Australia[6, 7] with one from each of the following countries: Northern Ireland,[13] Canada,[12] New Zealand[47] and Ireland.[35] Nine documents were sourced from the U.S.A.[3-5, 129-133, 137] Most were general IPC guidelines with some having a focus on particular health and care settings, such as primary care[35, 128] or care homes.[10, 130, 132] Some applied to a particular group of pathogens for example multidrug resistant organisms (MDROs)[131, 132] or acute respiratory tract infections.[2, 9]

Guidance outlines that TBPs are to be used in addition to standard precautions, for patients known or suspected to be infected or colonised with specific pathogens.[1, 3, 13, 47, 128, 129] Guidance from the WHO, CDC, Australia and Canada states that TBPs are initiated based on the presenting symptoms of the patient and suspected infective agent, with modifications being made, if necessary, following formal diagnosis.[1-3, 7, 12]

3.8.1 Pathogen type/severity of illness

Guidance consistently advocates the use of specific sets of TBPs (contact, droplet or airborne) based on the transmission mode of the assumed or confirmed presenting pathogen (contact, droplet or airborne). Most guidance states that contact precautions should be used for pathogens transmitted via direct and indirect contact,[3, 5-7, 9, 13, 129, 131, 132] that droplet precautions should be used for pathogens spread by the droplet route or large respiratory droplets and that airborne precautions should be used for pathogens transmitted via the airborne route[3, 5, 7, 9, 12, 13, 129]

In addition to use of the contact, droplet or airborne pathogen framework, many organisations highlight that TBPs are required for pathogens where standard precautions alone are deemed insufficient for the prevention of nosocomial transmission.[3, 6, 7, 9, 10, 12, 13, 129, 132] Support of this statement through citation of primary studies is challenging. Observational studies and outbreak reports, such as those cited in one CDC guidance document[138-140] cannot distinguish between precautions that are implemented in line with either SICPs or TBPs, or account for the potential effect of TBPs compensating for poor SICPs adherence.[3] To support the need for TBPs (purely from a scientific evidence-based point of view) it should be demonstrated that, where there is an increased risk of transmission, SICPs alone do not provide adequate protection.

In guidance, descriptions of pathogens for which TBPs should be applied are not always based on transmission mode alone. Canadian guidance states that contact precautions should be considered "for microorganisms of very low infective dose" therefore inferring a greater risk of transmission relative to other pathogens.[12] The CDC and Canadian PHA recommend use of contact precautions for patients known to be infected or colonised with epidemiologically important multi-drug resistant organisms[12, 137] sometimes referred to as 'novel' or 'targeted' MDROs.[130] This represents a focus on severity of outcomes for patients, not transmission routes. Australian guidance highlights that TBPs are particularly important for controlling the spread of MDROs but do not cite supportive evidence.[7] Both the WHO and Canadian PHA use the term 'epidemiologically significant' pathogens.[1, 12] The UK Department of Health and Social Care and Canadian PHA state that additional precaution requirements should be based not only on the pathogen's mode of transmission, but the severity of the illness it causes.[10, 12]

3.8.2 TBP indications beyond pathogen type

Beyond pathogen type, guidance outlined that increased risk of transmission would reflect a need for TBPs and was connected to local outbreak data, [2, 3, 7, 12, 131, 132] the nature of the medical procedure/task being undertaken,[2, 10, 12] as well as patient factors such as age,[12] symptomology (for example, diarrhoea which cannot be contained)[3, 12] and/or the patient's ability to perform hand hygiene.[12, 131]

Further reflection of altered TBP practice based on a perceived increased risk can be seen in Canadian and UK Department of Health and Social Care guidance. Authors outline that before every patient interaction, healthcare workers should perform a point of care risk assessment (PCRA) to ensure that, if necessary, appropriate additional precautions are put in place.[10, 12] The UK Department of Health and Social Care's PCRA includes consideration of patient symptoms, the patient's history of contact with infectious sources, the patient's risk factors such as immunosuppression, and environmental risk factors.[10] Canadian guidance recommends the healthcare worker to consider what type of contact they are going to have with the patient, what kind of procedure/care activity is going to be performed, whether the patient's body fluids are contained, whether the patient is willing and able to perform hand hygiene and whether the patient is in a shared room.[12]

Guidance does not acknowledge the potential barriers to conducting a PCRA which may include, for example, not having information on environmental conditions such as ventilation rates and/or not being able to predict forthcoming medical interventions, especially in emergency situations.

3.8.3 Setting specific considerations

Some organisations emphasised that the specific health and care setting is an important consideration when implementing TBPs.[10, 12, 131] Canadian guidance stated that "application of additional precautions may vary between acute care, long term care, ambulatory care, pre-hospital care and home care settings" and that precautions which are "justified in terms of risk-benefit in an intensive care unit […] may not be of equal benefit or indicated for a patient in long term care".[12] Similarly the CDC provide setting-specific TBP guidance for patients colonised or infected with MDROs; in acute care settings they advocate use of contact precautions whereas for home care or ambulatory care settings, standard infection control precautions are recommended.[131] Within the ambulatory or home care setting, Canadian guidance does not recommend contact precautions for the care of MDRO patients with asymptomatic carriage.[12] No sources specified as to the exact reasoning behind setting specific caveats and no guidance sources specifically referred to ventilation levels as an indication for use of TBPs. The practicalities of implementing setting

specific TBPs would likely be challenging as patients may spend time in multiple areas/settings within a facility therefore a setting-specific approach may not be protective for all patients.

The CDC Enhanced Barrier Precautions (EBPs) approach is specific to the prevention of MDRO transmission in nursing homes and represents a set of setting and pathogen specific TBPs which involve consideration of patient factors.[4, 132] EBPs were outlined by the CDC in 2019. In 2021 the CDC expanded the indications for their application.[4, 130] In contrast to CDC contact precautions, where gloves and a gown are required for HCWs upon room entry and regardless of care activity, the CDC state that, unless required in line with standard precautions, EBPs involve the use of gown and gloves during "high-contact resident care activities" for a) residents with MDRO infection/colonisation or b) those at high risk of MDRO infection/colonisation for example residents with wounds or indwelling medical devices.[4, 132] 'High-contact' activities are those that "provide opportunities for transfer of MDROs to staff hands and clothing" and include changing linen, dressings, bathing/showering and device care or use (for example feeding tube, tracheostomy).[132, 133]

In summary, the overarching framework of contact, droplet and airborne precautions, based on transmission mode, does not adequately encompass the varied, complex, and multi-factorial decision-making that is advocated by extant international guidance. The current framework is pathogen focused, a limitation which guidance producing organisations have attempted to overcome by providing multiple caveats and alterations to IPC recommendations, making use of said framework somewhat redundant. Evidence from guidance indicates that selection of specific IPC precautions needs to be based on elements beyond pathogen type alone, for example patient, procedural and environmental factors and these are not easily assimilated into a one-size-fits-all IPC precaution groupings.

3.8.4 Aerosol Generating Procedures

The existence of 'aerosol generating procedures' demonstrates the inadequacy of the droplet/airborne dichotomy as specific circumstances, beyond pathogen type, are considered to lead to a change in transmission categorisation (droplet to airborne)

and thus the associated recommended precautions. The concept of high-risk aerosol generating procedures (AGPs) arose following the study of Severe Acute Respiratory Syndrome (SARS) where an increased transmission risk to healthcare staff was observed in association with specific medical procedures such as intubation. Transmission patterns associated with these procedures were deemed to be more akin to those seen with 'airborne' pathogens and thus the higher risk was attributed to increased generation of small particles. In 2014, as part of their epidemic and pandemic acute respiratory infection guidance, the WHO stated that high risk AGPs are "medical procedures that have been reported to be aerosol-generating and consistently associated with an increased risk of pathogen transmission".[2] They provided further detail on the hypothesised mode of aerosol production by stating that "aerosols are produced when an air current moves across the surface of a film of liquid, generating small particles at the air–liquid interface. The particle size is inversely related to the velocity of air. Therefore, if a procedure causes air to travel at high speed over the respiratory mucosa and epithelium, the production of aerosols containing infectious agents is a potential risk".[2] However, no citations are provided to support this description. Canadian guidance[12] states that AGPs "generate aerosols as a result of artificial manipulation of a person's airway" and describes them as creating a high volume of "smaller infectious droplets" which can "travel farther than those generated spontaneously from patients". Authors cite a modelling study and narrative review to support the latter two statements.[39, 141]

Different high risk AGP lists are presented across IPC literature and guidance with weak supportive evidence.[2, 9, 12] This review assesses the evidence base in relation to how particles and pathogens are released into the air from the respiratory tract. A full assessment of any increased rates of patient-to-healthcare worker transmission, which are linked to specific medical procedures, are out with the scope of this review. Research question seven aims to assess the available evidence regarding medical procedures, in the context of particle production only. Findings reported may provide evidence for whether a procedure is deemed to produce significant levels of aerosol but cannot provide evidence on the relative infection risk associated with the procedure.

3.8.5 Evidence for efficacy of TBP bundles

Twenty-one primary research studies and five systematic literature reviews were critically appraised as part of this review however only one interrupted time series study and one retrospective cohort study (both graded SIGN50 level 3) were of high enough quality to merit inclusion in the assessment of contact precaution bundle efficacy.[135, 136] Studies were excluded based on a range of significant limitations including 1) poor or absent comparisons between before/after patient populations and/or settings 2) ill-defined descriptions of the specific contact precautions that were implemented 3) concurrent introduction of other IPC interventions and 4) significant differences between the before/after patient populations and/or settings. Although included in this review as SIGN50 level 3 evidence, both of the included studies results should be interpreted with caution as there remains a significant risk that the observed effects were not related specifically to the implemented contact precautions alone.[135, 136] In summary the evidence base regarding contact precautions is lacking in quantity and quality. An evidence-based conclusion regarding the efficacy of contact precautions cannot be made at this time.

3.9 Are there reported occurrences of person-to-person pathogen transmission which do not align with their currently assigned transmission mode(s)?

Three outbreak reports were identified as relevant to this research question and were graded as level 3 in accordance with the SIGN50 methodology.[142-144]

It is widely accepted that the transmission mode for *Acinetobacter baumannii (A.baumannii)* is contact, however, authors of an outbreak report involving a UK intensive care unit, hypothesised that transmission had occurred via transfer of contaminated air from the positive pressure operating theatre to the patient rooms via the shared ICU corridor or that indirect transmission had occurred via equipment that was contaminated via air flow from the same theatre.[142] Twenty-three sites across the unit were sampled using settle plates, or surface swabbing (both equipment and environmental surfaces). Across two rounds of sampling, five samples were positive for the outbreak strain of *A. baumannii*; a settle plate from a

trolley in the ICU corridor, a swab from the wheel of a trolley stored in the same corridor as well as an aromatherapy unit, shower head and shower hosing, all from the same patient room.[142] Contact tracing found that index patients had undergone treatment in the operating theatre seven days before one of the secondary case patients, during which time decontamination of the theatre was undertaken. Between environmental sampling results and contact tracing information, it was concluded that transmission most likely occurred via the shared corridor.[142] This study had many limitations including a lack of active air sampling and most notably, that no details were provided on shared portable equipment or staff. Presence of *A. baumannii* in the air of the shared corridor is demonstrated but whether this contributed to transmission in this outbreak is unclear.[142]

Long range air-mediated transmission of SARS-CoV-2 was hypothesised within two outbreak reports. One report hypothesised long-range air mediated transmission to at least one patient who had no reported significant contacts with other infected patients during a nosocomial outbreak.[143] An air flow investigation revealed a faulty air duct between a shared bathroom and this patient's room. Whole genome sequencing confirmed that for the nine cases involved in the outbreak, eight SARS-CoV-2 strains were 100% identical, including the patient to whom long-range transmission was hypothesised.[143] Environmental sampling was not undertaken and no information was reported on shared healthcare workers. A brief interaction between the patient, for which long range transmission was suspected, and another SARS-CoV-2 patient was described where both were within a shared utility room for 30 seconds while wearing masks.[143] The patient case for which long range transmission was suspected was also reported to have "stopped by the shared utility room once or twice daily to deliver his food plate". These activities cannot be excluded as possible transmission opportunities.[143]

The other outbreak report which hypothesised long range air-mediated transmission of SARS-CoV-2 was associated with a paediatric ward in Israel, with a single patient source and 12 secondary cases (three patients and nine HCWs).[144] Physical distancing and PPE measures (surgical masks) were reportedly in place during this outbreak. All patients remained 6ft from the index patient and three of the positive HCWs reported no direct contact with index patient.[144] No environmental testing was

undertaken to rule out indirect contact transmission, no WGS was undertaken to link cases and reporting of compliance to control measures was based on post-outbreak staff reporting.[144]

Reports of pathogens being transmitted by modes beyond the widely accepted or cited route within health and care settings are rare. The included outbreak reports represent low-quality evidence sources and have numerous limitations including limited information regarding movement of HCWs and other staff. Conclusions are based mainly on circumstantial evidence.

3.10 What factors should be considered when determining whether to discontinue TBPs?

Recommendations regarding ceasing TBPs are likely to be highly pathogen and/or infection specific with variability in infectious periods, symptoms, and infection severity. Conducting an extensive search and appraisal process for all pathogens individually, was out with the scope and resource of this initial review.

Nineteen pieces of evidence were identified as relevant to this research question; one systematic review (SIGN50 level 1+),[145] three cohort studies[146-148] (all SIGN50 level 3) five observational studies[90, 149-152] (all SIGN50 level 3) and 10 expert opinion pieces[2-4, 7, 9, 12, 131, 153-155] (all SIGN50 level 4).

The literature outlined that discontinuation of TBPs may be dependent upon factors such as:

- the type of infective pathogen[2, 3, 9, 12, 153, 154]
- the period of infectivity (estimated based on testing results or pathogen related evidence base)[3, 9, 90, 131, 147, 153, 154]
- the estimated timing of the infectious period for example when pre-symptomatic[9, 153]
- pathogen clearance times[146, 148]
- the possibility of infection recurrence[146, 148]
- the possibility of prolonged carriage[9, 147, 148]

Estimated end of infectious period was linked to specific indicators such as symptom resolution,[4, 9 7, 153, 155 3, 12] a set period of time having elapsed following treatment end,[153-155 12] a set period of time having elapsed following symptom onset/resolution[3, 12, 153-155] or testing results.[3, 9, 12, 131, 147, 152, 154] However, estimating period of infectivity can be challenging as it can vary depending on patient age, immune status, and presence of co-infection.[2, 3, 9, 12, 145, 149, 154] It was noted by the Public Health Agency of Canada, as part of an expert opinion, that it is the responsibility of clinical staff to ensure that patients are not cared for under unnecessary precautions, to review precautions regularly, and to discontinue precautions when they are no longer required.[12]

Regarding MDROs, the CDC stated that based on the 1995 HICPAC guidelines, discontinuation of contact precautions for patients with vancomycin-resistant *enterococci* (VRE) infection should only occur after three successive weekly negative stool or perianal cultures.[131] This trigger for discontinuation was extended to all MDROs when the patient had not received antimicrobial therapy for several weeks and there was no indication of ongoing MDRO transmission within the health and care facility.[131] Similarly, Banach et al presented recommendations for MRSA and VRE that included obtaining between one to three negative screening cultures and maintaining precautions for a longer period of time for high-risk patients.[154] High risk patients were defined as those who: are highly immunosuppressed, have chronic wounds, reside in long-term care facilities, are receiving broad spectrum systemic antimicrobial therapy and/or are receiving care in protected environments (for example burn units).[154] This standpoint on cultures for MDROs and extension of precautions for high-risk patients, was also shared by the CDC.[3] In another CDC expert opinion piece, authors reported that based on current available evidence, a definitive indication for discontinuation of contact precautions for patients infected or colonised with MDROs could not be presented.[131]

Symptom based discontinuation triggers were outlined in multiple papers. A general rule of maintaining precautions for 24 hours following resolution of fever or respiratory symptoms is presented by PHE, specifically when discussing influenza.[9] For other prolonged illnesses, for example pneumonia, PHE advised that precautions should be continued for the duration of acute illness and should only be

discontinued when symptoms have resolved.[9] It is noted by Australian Government guidelines that TBPs should only be in place for limited periods of time. Usually until symptoms have resolved or by recommendation of IPC professionals.[7] Similarly, the World Health Organization state that the duration of precautions should be dictated by the duration of symptomatic illness.[2] Regarding *C. difficile*, Banach et al recommend that precautions should be maintained until at least 48 hours after resolution of diarrhoea.[154]

In contrast with symptom-based decision making, the CDC focus on wound healing and device use. Within their FAQs regarding the use of enhanced barrier precautions in nursing homes, the CDC suggest maintaining enhanced barrier precautions for the duration of a resident's stay or until wounds have resolved, or indwelling devices are removed.[4]

Contradiction regarding TBP discontinuation indications and triggers are found throughout the literature. Most notably, the WHO state that laboratory tests should not routinely be used to determine when precautions should be discontinued due to lack of evidence on their efficacy.[2] Observational studies were identified which reflected this concept, as testing policies (in place to trigger discontinuation of TBPs) were found to be inadequate in identifying when patients no longer required precautions.[150, 151] Authors reported false negative test results and HCW glove contamination with the infectious agent after the discontinuation of precautions.[150, 151]

Where it is recommended that transmission-based precautions only be implemented for a limited period, there is often an accompanying requirement that a plan for discontinuation or de-escalation be in place from the outset.[4, 154]

It can be concluded from the available relevant evidence that the decision to discontinue transmission-based precautions is complex and cannot be generalised across all pathogens or all patients.

4. Implications for research

Standardisation of terminology is needed regarding the description of potentially infectious particles, for example droplets, droplet nuclei and aerosols. Aside from being evidence based, terminology should be intuitive and adaptable to the multitude

of settings in which it might be used. Particle size must be considered alongside viability, infectious dose and environmental conditions. Evidence for presence of viable pathogens in small particles does not directly indicate that these particles are responsible for transmission.

Further evidence is needed on the value and efficacy of transmission-based precaution bundles. Regarding contact precautions, current evidence can neither support nor invalidate the approach of using a combination of isolation and universal gloving and gowning for certain pathogens. High quality controlled, randomised studies with monitoring of adherence are needed, to assess their efficacy in comparison with standard precautions.

The challenge of conducting air sampling studies must be acknowledged as well as the efforts of those who performed data gathering during the COVID-19 pandemic. Investigators conducted challenging studies in an attempt to further the understanding of a novel pathogen, all the while trying to limit disruption of essential health and care services.

More high-quality studies which establish the distances travelled by viable pathogens are needed to facilitate identification of 'at risk' zones within health and care settings. The studies identified as part of this review frequently failed to assess influence of air currents, report on whether participants maintained specified distances from air samplers or specify the types of medical/care procedures undergone by participants at time of sampling. Studies also frequently failed to test others who may have contributed to the air sample, which was especially important during COVID-19 pandemic associated studies. Across the evidence base for particle/pathogen production, larger sample sizes were needed especially considering the wide inter-subject variation that was frequently identified. Standardisation of certain parameters (e.g., ventilation rates, temperature, humidity, subject activities) across studies would facilitate comparison of data.

Very few studies of sufficient quality were identified in relation to pathogen clearance times within defined air spaces. Findings from this form of research would be essential in supporting recommendations regarding fallow times.

Studies which aimed to assess whether certain medical procedures generated large amounts of small particles often used inappropriate baseline measurement comparators. Ideally, particle counts should be compared between a procedure and a simulated scenario where every part of the procedure is repeated without the hypothesised 'aerosol generating' element of interest included. Due to high inter-subject particle production variability, using subjects as their own controls is prudent, but if not possible or appropriate, large sample sizes will be required to mitigate the effect of variability amongst the study cohort.

Regarding respiratory activities and medical procedures, particle counts being used as a proxy for infection risk needs to be scrutinised. Studies by Viklund et al and Dinkele et al suggested that there may not be a direct correlation between airborne particle counts and viral or bacterial load emitted.[116, 120]

Further research regarding the source of airborne particles and pathogens would be beneficial. Knowing whether infective pathogen carrying particles originate solely, partly or mostly from the respiratory tract as opposed to external factors such as linen movement, skin shedding etc. will support IPC source control-based recommendations. Bischoff's 2004 study involving individuals who were colonised with coagulase negative *staphylococci* (CoNS) bacteria, both in their noses and on their skin, suggested a predominant non-respiratory tract source of bacteria.[76] Sterile clothing significantly reduced CoNS (CFU/ m3/min) dispersion in the air, when compared with own clothing ($p<0.0001$). In contrast, authors found no significant decrease in CoNS bacteria dispersal by adding a mask to the participant's ensemble ($p=0.433$).[76]

It is acknowledged that many of the exclusion criteria represent important limitations of this literature review. As per the NIPCM development process, evidence from non-healthcare settings is excluded as part of the NIPCM literature review exclusion criteria. Inclusion of non-healthcare settings was considered for this literature review but was not possible due to time and resource limitations.

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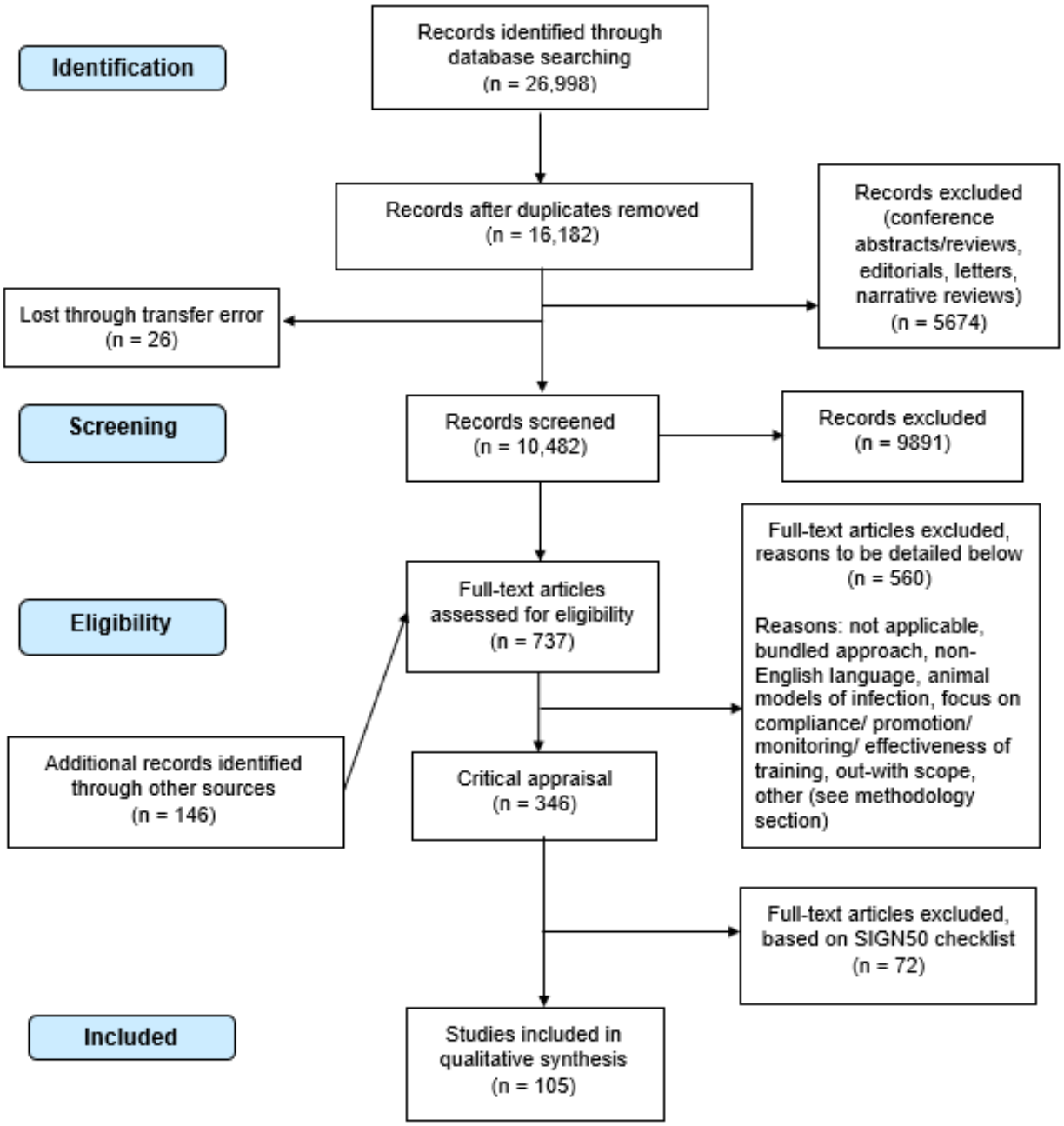
Appendices

Appendix 1: SIGN50 Grades of Evidence

Grade	Description
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, for example case reports, case series
4	Expert opinion

Appendix 2: PRISMA flow diagram



Appendix 3: Characteristics of air sampling studies involving pathogen detection (40 studies)

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
59. Lednicky et al 2020	Viable SARS-CoV-2 virus	Single hospital room with curtain dividing two patients. 6 ACH.	One COVID-19 infected patient. Positive test one day before sampling. Authors report no AGPs, other medical interventions not reported. Patient experienced "respiratory illness" - specific symptoms unclear. Activities or movement during sampling unclear.	2 days (N/A)	Small amounts of viable SARS-CoV-2 virus detected at 4.8m. No particle size assessment.
111. Johnson et al 2022	Viable SARS-CoV-2 virus and SARS-CoV-2 RNA.	In participant homes, garages or	17 COVID-19 infected participants Mean age:	Within last 6 days	SARS-CoV-2 viral RNA was detected in air samples at

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
		backyards (n=12 subjects) In inpatient setting (standard ward-room) (n=5 subjects) Not highly relevant as sampling into cone shaped aperture at close range.	50.8years. Participants identified from recent NP swab (taken immediately prior to collecting air samples). Participants from community (n=12) or were hospital inpatients (n=5). Participants asked to breathe normally, speak (read a 330 word passage) and cough (voluntarily cough 5 repetitions of 5 forced coughs)		source (0.3-10μm) (17 participants) and in the 0.65-7μm size range (4 participants). Viable SARS-CoV-2 virus was shown to be disseminated into the immediate environment via coughing (two participants).
73. Santarpia et al 2021	Viable SARS-CoV-2 virus and SARS-CoV-2 RNA	Six single hospital rooms (2 rooms were isolated from	6 hospitalised, COVID-19 infected pts. All but one had cough symptoms.	2, 3 and 10 days post first positive test.	SARS-CoV-2 RNA was detected in all three particle size groups (<1μm, 1-

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
		ward and negatively pressured)	Unclear as to activity of subjects or medical interventions during sampling.		4µm and >4µm) at the end of each subject's bed. Viable SARS-CoV-2 was detected in <1µm size fractionated samples from the end of three subjects' beds (stated to be at least 1m).
67. Shankar et al 2022	SARS-CoV-2 RNA	Subject's apartments	Two COVID-19 infected subjects. Subject 1 tested positive 8 days before sampling. Subject 2 tested positive 6 days before sampling. Both subjects had mild cough. Subject 2 was co-infected	Subject 1 – 4 days (N/A) Subject 2 – 9 days (N/A)	Subject 1 - SARS-CoV-2 RNA detected in particles >4.4µm at 1.8m. Subject 2 – SARS-CoV-2 RNA detected in particles <1µm at 2.2m.

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
			with adenovirus. Unclear as to subject movement/activities during sampling.		
72. Binder et al 2020	SARS-CoV-2 RNA	Single hospital room, ~14 ACH.	13 hospitalised patients. Lab-confirmed COVID-19 infection (clinical samples taken at enrolment, unclear if this aligned with time of air sampling). Mean age was 56.2 (range 29-91) Pts 1 and 2 – cough, fatigue and difficulty breathing Pt 3 – runny nose, fever and headache	8.7 days (1-21 days)	SARS-CoV-2 RNA detected in relation to 3 patients. Pt 1 - RNA detected at 1.4m in particles <4.4µm. Pt 2 – RNA detected at 2.2m in particles <4.4µm Pt 3 – RNA detected at 2.2m in particles >4.4µm

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
104. Chia et al 2020	SARS-CoV-2 RNA	Hospital airborne isolation rooms (12 ACH)	3 COVID-19 infected patients. All had cough symptoms. PCR tests conducted within 72 hours of air sampling. No patients needed supplementary oxygen or underwent AGPs 24 hrs prior.	Pt 1: 9 days Pts 2 and 3: 5 days	SARS-CoV-2 RNA detected at 1m from 2 COVID-19 infected patients (pts 2 and 3) in particles of sizes >4µm and 1-4µm.
105. Ong et al 2021	SARS-CoV-2 RNA	Twelve hospital airborne isolation rooms (12 ACH). Eight rooms housed two patients, four rooms were single occupancy.	19 COVID-19 infected subjects. No subjects needed supplementary oxygen or underwent AGPs 24 hrs prior.	5.8 days (3-11)	Six out of 12 rooms had positive SARS-CoV-2 RNA samples, in four of which, samples were restricted to particles sized <4.34µm. Samples were taken 1m away from subjects. Two of the six rooms were

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
					single occupancy and four were double occupancy.
106. Coleman et al 2021	SARS-CoV-2 RNA	Unclear	22 COVID-19 infected subjects. Three sampling conditions: 30 mins of breathing, 15 mins of talking and 15 mins of singing.	4.18 days (-2-9)	13 subjects (59%) emitted detectable levels of SARS-CoV-2 RNA in respiratory aerosols, including three asymptomatic and one pre-symptomatic subject. Overall, fine aerosols (≤5μm) constituted 85% of the viral load detected
114. Kim et al 2020	SARS-CoV-2 RNA	- 2 pts from hospital A (AIIR with min 15ACH)	8 hospitalised Covid-19 infected patients	Air samples taken 3, 5 and 7 days post admission. All patients were admitted within 7	All 52 air samples were negative at 2m from patients.

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
		- 1 pt from hospital B (AIIR with min 15ACH) - 2 pts from hospital C (isolation rooms, no neg air pressure) - 3 pts from hospital D (cohorting, no neg pressure, all 3 pts shared a room containing five beds)		days of symptom onset meaning air samples could represent results based on 3-14 days post symptom onset.	
115. Alsved et al 2022	SARS-CoV-2 RNA	Mobile van. Not highly relevant as sampling into cone shaped aperture at close range.	38 COVID-19 infected subjects. Breathing, talking and singing.	≤6 days of symptoms	SARS-CoV-2 RNA detected in the exhaled breath of 19/38 subjects at less than 1m during breathing, speaking and singing. RNA was detected in samples from small

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
					particle size bins (1–4 µm and <1µm).
116. Viklund et al 2022	SARS-CoV-2 RNA	Unclear. Not highly relevant as sampling via mouthpiece.	25 COVID-19 infected subjects. Confirmed positive by rapid antigen test and NP swab PCR test, both taken on day of sampling. Normal breathing (2 mins). Deep breathing (5 mins). 3 x forced coughs.	2 days (0-9)	SARS-CoV-2 RNA was detected for 10 subjects in exhaled particles of <5µm in size when breathing, coughing or performing a deep exhalation/rapid inhalation manoeuvres.
118. Akin et al 2022	SARS CoV-2 RNA	12m^2 operating room	24 COVID-19 infected subjects, 12 in group A and 12 in group B. Both groups underwent 10 mins of ultrasonic scaling and 5 mins of non-contact tooth	0-5 days post diagnosis.	Settle plates were positive for 5 patients. Two plates were positive at 0.9m and two at 2.53m. One plate was positive at 1.2m and 3.1m.

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
			drilling. Group A: Medium volume suction Group B: high volume suction		
119. Gohli et al 2022	SARS-CoV-2 RNA	"Room was naturally ventilated with a single ventilation shaft, and by briefly opening the outside entrance between trials."	14 COVID-19 infected subjects. All mildly symptomatic. Tested positive for SARS-CoV-2 within 5 days of sampling.	6 days (2-15)	SARS-CoV-2 RNA was detected in air at 1m and 2m from infected subjects whilst talking for 15 minutes. RNA was detected at 4 m from a zone which hosted 8 infected subjects for approx. 2 hours and 40 mins.
121. Sawano et al 2021	SARS-CoV-2 RNA	Special quarantine ward	48 COVID-19 infected, hospitalised patients. Median age = 53 [(QR, 43.8-64.3) with a positive diagnosis of COVID-	5 days (IQR 3-7)	Viral RNA detected in 15 EBC samples from 12 patients.

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
			19 following PCR positive NP swab sample – unclear when this was taken in relation to sampling. Breathing for 5-7 mins. Nine with radiologically evident pneumonia. Nine required oxygen and three required mechanical ventilation.		
60. Lindsley et al 2016	Viable influenza	Unclear. Not highly relevant as sampling via mouthpiece.	58 influenza infected, otherwise healthy, college students. NP swab taken on day of sampling. Mean age 21 (SD 3.4). Three forced coughs and three deep	2.2 days (SD 2.1)	Viable influenza detected in cough samples (28/53) and in positive deep inhalation/rapid exhalation samples (22/52) at source.

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
			inhalation/rapid exhalations.		
65. Lindsley et al 2010	Viable influenza	Unclear. Not highly relevant as sampling via mouthpiece.	21 symptomatic influenza infected students. Infection confirmed through NP swabs taken on day of sampling.	~2 days (SD 5)	Viable influenza detected in cough exhalations of two students at source.
74. Yan et al 2018	Viable influenza and influenza RNA	Unclear. Not highly relevant as sampling into cone shaped aperture at close range.	142 symptomatic influenza infected subjects. Young adults, 19-21yo. Infection lab confirmed on day of sampling. Variable cough frequency during sampling (IQR 5-39) High asthma prevalence in cohort (21%). Sampling involved	All within first 3 days of symptom onset.	Viable influenza detected at close range (<1m) in 30 mins of speech and breath exhalations in 52/134 samples (unclear number of subjects) in particles <5µm. Influenza RNA detected at close range (<1m) in 30 mins of speech and

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
			30 mins of breathing and speaking.		breath exhalations in particles >5 (88/218 samples) and <5µm (166/218 samples). Unclear number of subjects.
77. Milton et al 2013	Viable influenza and influenza RNA	Unclear. Not highly relevant as sampling into cone shaped aperture at close range.	37 influenza infected symptomatic subjects, median age of 19. NP swabs taken on day of sampling. 30 minutes of breathing and coughing (30 x cough)	2 days[a] (0-5 days)	Viable influenza was detected in breathing and coughing exhalations for 2 of 27 subjects at close range (<1m) in fine particle samples (<5µm). Influenza RNA was detected in both coarse (>5µm) and fine (<5µm) particle samples for 16/37 and 34/37 participants

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
					respectively at close range (<1m). Small particles (<5µm) carried the majority of influenza RNA within 1m of source.
65. Lindsley et al 2010	Influenza RNA	Unclear. Not highly relevant as sampling via mouthpiece.	38 symptomatic influenza infected students. Infection confirmed through NP swabs taken on day of sampling. Age range 18-33. Three forced coughs.	~2 days (SD 5)	Influenza RNA detected in cough exhalations of 32 subjects at source. For 26 subjects RNA was detected in particles <4µm in size. 65% of influenza RNA was found in particles of <4µm in size.
88. Killingley et al 2016	Influenza RNA	Single hospital rooms or community bedrooms. Rooms	12 symptomatic, influenza infected subjects (9 adults	All within first 4 days of symptom onset	Influenza RNA was detected at 1-2m

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
		with positive air samples were 17-23.3°C and 44-50% relative humidity.	and 3 children). Lab confirmed infection n day of air sampling. Unclear as to subject activities or medical interventions during sampling.		from 3 subjects in particles <4µm.
90. Killingley et al 2010	Influenza RNA	Single hospital rooms or community bedrooms. Temperatures ranged from 20-23.3°C. Relative humidity ranged from 50-64%.	3 influenza infected subjects (1 adult and 2 children). Lab confirmed infection on day of air sampling. Unclear as to subject activities or medical interventions undergone during sampling.	3.3 days (3-4)	H1N1 influenza RNA was detected in particle size ranges <1 (1 subject), 1-4, (2 subjects) and >4µm (1 subject) within the air at approximately 0.9m from 2 infected subjects.
112. Yip et al 2019	Influenza RNA	Single hospital rooms (4-6 ACH)	16 hospitalised, influenza infected patients (lab	Not reported	Influenza virus RNA was recovered >1 room air samples

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
			confirmed within 48 hrs). One pt was reported to require mechanical ventilation and nine required oxygen therapy, it is unclear if this was ongoing during sampling and whether this applied to the positive sample cases.		from 6 of 13 (46%) participants with influenza A in at least one of the three size ranges (<1 μm, 1–4 μm and >4 μm) and at 2m in 2 cases.
70. Bischoff et al 2016	Measles virus RNA	Single, negative pressure isolation hospital room, 6 ACH.	Single hospitalised, measles infected, but otherwise healthy, patient. Tested positive on every day of sampling. Minor coughing episodes on day 5 PRO, moderate coughing	5 to 8 days PRO (sampling conducted on each day)	MeV RNA detected in particles <4.7μm at 0.61m, 0.91m and 2.4m on days 5 and 7 post rash onset/admission.

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
			on days 6 and 7 PRO. Medical interventions not reported.		
75. Bischoff et al 2006	Viable *Staphylococcus aureus*	Airtight chamber (3.1m^3 built around the front of a class II biological safety hood)	11 students (19-29yo) with S. aureus nasal carriage. Sneezing/non-sneezing. Pre and post artificial inoculation with rhinovirus.	N/A. Nasal carriage of S. aureus was established to have been present for 4 weeks through repeated testing. However, unclear how long between final NP swab and air sampling.	Viable S. aureus bacteria was detected in breathing and sneezing exhalations at a distance (~3m) in particles <5µm. Sneezing significantly increased the amount of S. aureus bacteria disseminated into the air.

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
76. Bischoff et al 2004	Viable Coagulase negative *staphylococci*	Airtight chamber (3.1m^3 built around the front of a class II biological safety hood)	12 subjects with CoNS nasal and skin carriage. 20-37yo. Artificial inoculation with rhinovirus. Pre and post inoculation air samples. Samples taken with subjects wearing own clothes or in sterile garb and with and without facemask.	N/A. Nasal carriage of CoNS was established to have been present for 4 weeks through repeated testing. However, unclear how long between final NP swab and air sampling.	Viable Coagulase-negative Staphylococci (CoNS) bacteria was detected in breathing exhalations at distance (~3m) in particles <5µm. Sterile clothing significantly reduced CoNS (CFU/ m3/min) dispersion in the air, when compared with own clothing ($p<0.0001$). Authors found no significant decrease in CoNS bacteria dispersal by adding a mask to the participant's ensemble ($p=0.433$).

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
83. Kulkarni et al 2016	Viable respiratory syncytial virus	Cubicles in general paediatric ward (n=15 pts, 6 ACH) and ICU ward (n=3 pts, 10 ACH)	18 RSV infected, hospitalised, paediatric patients. Mean age 47 weeks. Lab confirmed RSV infection but unclear how long before air sampling clinical samples were obtained. 3/17 pts were ventilated, with associated open suctioning, and 6/17 were receiving oxygen via nasal cannula. 2 had co-infection with Influenza H1N1.	7.9 days (range 2-19)	Viable RSV was detected at 1m from 17 of 18 paediatric patients in particles <4.7µm and <1.1µm. Study also demonstrated that 2 hrs following discharge of 3 pts from cubicles viable virus was still detectable in the air, although reduced. It is unclear what procedures these patients underwent.
94. Gralton et al 2013	Parainfluenza RNA and rhinovirus RNA.	Non-isolation hospital rooms,	12 adults (2 asthmatic) and 41	All but one subject had experienced	Parainfluenza RNA (13/53) and hRV

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
		infectious diseases ward. Not highly relevant as sampling via mouthpiece.	children (28 asthmatic) 52 subjects provided breathing samples 50 subjects provided cough samples.	symptoms in 24 hour period before sampling.	RNA (24/53) was detected in the exhalations of 13 and 24 subjects respectively within both small (0.65-4.7μm) and large particles (>4.7μm) whilst breathing and coughing. There was no significant difference regarding frequency of viral RNA detection between breath (10 minutes) and cough samples (10 x coughs) (p= 0.712)
95. Wood et al 2019[b] (A)	Viable *S. aureus* and gram-negative bacteria	Enclosed rig of 4.5m perspex tunnel with HEPA-filtered airflow.	Cystic fibrosis patients with either a history of S. aureus respiratory infection	N/A	14 of 18 GNB strains were detected at 2m and 11 of 18 at 4m.

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
			(n=16) or a history of GNB respiratory infection (15 subjects, 18 strains). Sputum samples taken on day of sampling to confirm infection/ colonisation Coughing samples (5 mins)		S. aureus was detected for 9 of 16 subjects at 2m and 8 of 16 subjects at 4m. A correlation was identified between bacterial sputum and aerosol concentrations at two metres for both GNB species (r=0.50, p=0.035) and S. aureus (r=0.66, p=0.005)
95. Wood et al 2019[b] (B)	Viable *S. aureus* and gram-negative bacteria	Duration rig. Not highly relevant as sampling via mouthpiece.	Cystic fibrosis patients with either a history of S. aureus respiratory infection (n=16) or a history of GNB respiratory infection (n=15). Coughing samples	N/A	9 of 17 GNB strains were viable at 45 mins and 4 of 16 S. aureus strains were viable at 45 mins.

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
			(2 mins). Sputum samples taken on day of sampling to confirm infection/ colonisation		
96. Stockwell et al 2019 (A)	Viable *P. aeruginosa*	Enclosed rig with HEPA filtered airflow	12 subjects with COPD and/or bronchiectasis AND positive P. aeruginosa sputum samples. Sputum samples taken on day of sampling to confirm infection/ colonisation Coughing samples (5 mins)	N/A	Viable P.aeruginosa was detected at 2m from 5 subjects and 4m from 4 subjects..
96. Stockwell et al 2019 (B)	Viable *P. aeruginosa*	Duration rig. Not highly relevant as sampling via mouthpiece.	6 subjects with bronchiectasis and positive P. aeruginosa sputum	N/A	Viable P. aeruginosa detected for 2 of 6 subjects at 15 mins post cough

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
			samples. Sputum samples taken on day of sampling to confirm infection/ colonisation Coughing samples (2 mins)		production. No positive aerosol samples at 5 or 45 mins.
97. Knibbs et al 2014 (A)	Viable *P. aeruginosa*	Distance rig with HEPA filtered air.	18 cystic fibrosis patients chronically infected with P. aeruginosa. Mean age 25.8. Sputum samples taken on day of sampling to confirm infection/ colonisation Coughing sample (5 mins)	N/A	Viable P. aeruginosa was isolated at 4m from 17/18 participants (94%). Positive aerosol samples were associated with both small (<3.3µm) and large (>3.3µm) particle size fractionated samples
97. Knibbs et al 2014 (B)	Viable *P. aeruginosa*	Duration rig. Not highly relevant as sampling via	18 cystic fibrosis patients chronically infected with P.	N/A	Aerosols containing P. aeruginosa remained viable at 5

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
		mouthpiece. 0.4m^3 airtight stainless-steel cylinder was rotated at 1.7 rpm	aeruginosa. Sputum samples taken on day of sampling to confirm infection/ colonisation. Mean age 25.8. Coughing sample (2 mins)		minutes from 15 participants, at 15 minutes from 14 participants and at 45 mins from 14 participants. Positive aerosol samples were associated with both small (<3.3µm) and large (>3.3µm) particle size fractionated samples.
91. Wainwright et al 2009	Viable *P. aeruginosa* and viable *B. cenocepacia*	Consultation rooms, mean ACH ranged from 9.7-19.4. Not highly relevant as sampling via mouthpiece.	21 cystic fibrosis patients colonised with *P.aeruginosa* and/or *B.cenocepacia* (12 adults, 14 children). Coughing for 5 mins. Sputum samples	N/A	20 patients who cultured *P. aeruginosa* in their sputum also cultured *P. aeruginosa* of similar genotype in their cough exhalation samples at source. 71.8% of

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
			taken 12 days before sampling.		culturable particles were <3.3µm. *B. cenocepacia* was cultured from the at source cough sample provided by the patient who had *B. cenocepacia* isolated from their sputum.
92. Wood et al 2018	Viable *P. aeruginosa* and viable *S. maltophilia*	Unclear. Within closed wind tunnel system.	24 Cystic fibrosis patients with chronic P. aeruginosa infection. Coughing for 5 mins. Talking for 5 mins.	Sputum samples taken on day of sampling.	Viable *P. aeruginosa* was detected at 2m in cough exhalations from 19 participants. 71% of culturable particles (from coughing) were <4.7µm. 3 individuals with *S. maltophilia* in their sputum generated aerosols that grew

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
					this organism. There may be a correlation between sputum and cough *P. aeruginosa* CFU counts in cystic fibrosis (CF) patient cohorts (r=0.55, p=0.01). No aerosol CFUs were recovered from talking.
103. Ferroni et al 2008	Viable *P. aeruginosa* and viable *S. aureus*	Single hospital rooms. Described as closed environments.	Children hospitalised with cystic fibrosis. - 22 pts colonised with *P. aeruginosa* - 17 pts colonised with *S. aureus*	N/A	- 12/22 (50%) *P. aeruginosa* colonised patients had *P. aeruginosa* recovered from the air samples (In 6 cases, the strain was genetically identical in their sputum and air sample)

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
					- 6/17 *S. aureus* colonised patients had *S. aureus* recovered from the air samples (No strains identified in patient samples were identical to those isolated from air samples.) Distance from sampler unknown. Samples taken at three different times - waking up, after physiotherapy and after cleaning. The total number of bacteria was significantly higher at waking up and after physiotherapy than

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
					after cleaning (p=0.03 and p=0.005, respectively).
101. Choukri et al 2010	*Pneumocystis jirovecii* DNA	Conventional patient rooms with no negative pressure or laminar flow. Doors and windows kept closed.	15 pneumocystis pneumonia patients. 12 had HIV and 9 had received treatment 1-9 days before sampling.	1.3 days[c] (0-7)[c]	*Pneumocystis jirovecii* DNA was detected at 1m (13/15 subjects), 3m (9/15 subjects) and 5m (5/15 subjects) from patients. There was a significant decrease in fungal concentrations of samples collected at one metre and those collected at five metres (p= <0.05).
102. Frealle et al 2017	*Pneumocystis jirovecii* DNA	Single patient hospital rooms. Door	17 hospitalised immunocompromised patients diagnosed	N/A	*P. jirovecii* DNA detected at 1m from 3 patients.

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
		and windows kept closed.	with *P. jirovecii* pulmonary colonisation		
66. Fennelly et al 2004	Viable *M. tuberculosis*	Not highly relevant as sampling via mouthpiece. Negative pressure isolation room, 6 ACH.	16 subjects with TB. 9 had MDR TB, 2 had drug resistant TB and 5 had isolates susceptible to all drugs. 14 had cavitary lung disease. 13 had received treatment in the previous week. Sputum specimen AFB positive before referral or on admission – unclear precisely how long this was before sampling. Five minutes of coughing. Cough frequency	N/A. Symptom status of subjects not reported.	Viable Mtb detected in cough exhalations (5 mins) of 4 patients at source. Production of culturable aerosol associated with lack of treatment in preceding week(s) (p=0.007). Majority (90%) of particles released were within particle sizes 0.65-3.3µm.

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
			during sampling ranged from 1 to 227. Samples collected during sputum induction for 15 subjects – unclear what this involved beyond the subjects forced coughs.		
109. Fennelly et al 2012	Viable *M. tuberculosis*	Hospital room. Windows kept open. Fan used to deflect airflow from behind technician past the subject and out through windows.	101 TB patients. 90/101 were sputum AFB smear-positive. Coughing samples (5 mins). Unclear which patients were on treatment when sampling was undertaken.	Had recent positive sputum sample for Mtb (last 7 days) with confirmatory sputum sample before sampling.	Positive samples were collected from 28 subjects in six size fractionated samples from 0.65 to >7µm. Authors reported that 96.4% of culturable particles were in the size range 0.65-4.7 µm, with most falling within 1.1-2µm.

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
110. Jones-Lopez et al 2013	Viable *M. tuberculosis*	Unclear. Not highly relevant as sampling via mouthpiece.	96 TB patients. Sputum AFB smear-positive. 21 HIV infected (12 on antiretroviral therapy) Coughing samples (5 mins) Untreated or had received <5 days anti-TB treatment.	Median weeks of illness before enrolment was 12 with range of 8-20.	45% of TB infected subjects produced culturable Mtb when coughing. 19% of these subjects produced low aerosols (1-9CFUs) and 26% produced high aerosols (>10CFUs).
120. Dinkele et al 2022	Viable *M. tuberculosis*	Primary healthcare facility	38 symptomatic TB infected patients with GeneXpert-positive TB before treatment initiation. Sampling conducted during FVC, tidal breathing and coughing.	N/A	Tidal breathing produced significantly fewer Mtb per breath/manoeuvre compared to FVC and cough (2.6- and 3.2-fold respectively) but breathing is an ongoing, repeated daily activity compared to

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
					coughing which is sporadic. Within this study cohort, 1 minute of tidal breathing generated more bacilli than a single cough or FVC manoeuvre. All 3 manoeuvres returned similar rates of positivity for Mtb (65-70%),15 coughs/15 FVC manoeuvres/5 minutes of tidal breathing.
113. Kim et al 2016	Viable MERS CoV and MERS CoV RNA.	Single hospital rooms. Pts 1 and 2 were being treated at Hospital A which had rooms with ≥12 ACH. Air change	3 hospitalised MERS-CoV infected patients. Pts 1 and 2 positive via PCR testing up to day of sampling. Pt 3 last	Pt 1 – 22 days Pt 2 – 16 days Pt 3 – 19 days	MERS CoV RNA was detected 3-4m away from 2 patients and 2-3m away from another single patient. Viable

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
		rates for rooms of hospital B (pt 3) are not reported.	positive PCR test 6 days before sampling. Pts 1 and 2 both had pneumonia and were receiving mechanical ventilation at the time of sampling with endotracheal suctioning performed 30-60 mins before sampling. Pt 1 was receiving extracorporeal membrane oxygenation during sampling. No coughing or sneezing observed during sampling.		MERS-CoV was detected in air samples 3-4m from 2 patients.
122. Engel et al 2019	Viable *A. fumigatus*	Unclear.	Eleven cystic fibrosis patients colonised	N/A	Two patients had matching sputum

Reference	Pathogen/ outcome measure	Setting (confidence re: maintenance of distance to sampler)	Subjects	Mean days from symptoms until sampling (range)	Findings
			with A. fumigatus. Sputum samples collected on same day as sampling or within one month. Two coughs onto agar plates. Age range from 20-58 years.		and cough exhalation isolates.

a – median

b – In Wood et al's 2019 study (ref 113) the mean percentage of total bacteria cultured in <4.7µm particle size samples was 66.5% (SD 26.1) for the GNB organism group and 58.2% (SD 26.0) for the S. aureus group (p=0.46). It is unclear whether this finding was related to the distance (A) or duration (B) experiments.

c – days from diagnosis

Appendix 4: Studies excluded following critical appraisal

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